

**THE
BRITISH ENCYCLOPAEDIA
OF MEDICAL PRACTICE**

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**THE
BRITISH ENCYCLOPAEDIA
OF MEDICAL PRACTICE**

INCLUDING

**MEDICINE SURGERY
OBSTETRICS GYNAECOLOGY
AND OTHER SPECIAL SUBJECTS**

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VOLUME TWELVE

* TETANUS TO YELLOW FEVER

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THROMBOSIS OF CEREBRAL VEINS AND SINUSES

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1.-AETIOLOGY

1482.] Thrombosis of the cerebral veins and sinuses is caused either by the spread of sepsis from neighbouring structures, or without infection by alteration of the circulating blood. Although there are a number of deep and superficial cerebral veins and five unpaired and six paired dural sinuses, the superior group of superficial veins, the superior longitudinal sinus into which they drain, the lateral sinus, and the cavernous sinus are alone of practical import to the subject. *Vessels liable to thrombosis*

Infective thromboses may be encountered at any age and are chiefly associated with sepsis of the middle ear, the buccal and nasal cavities, the pharynx, or the integument of the face and scalp. General septicaemia and pyaemia or diffuse purulent meningitis are occasional causes. *Infective thrombosis*

Non-infective thrombosis, on the other hand, is related to any general disease, like acute gastro-enteritis which produces sudden severe depletion of the tissue-fluids, and is almost limited to infancy. *Non-infective thrombosis*

The average age in a series of cases collected by Byers and Hass was nine months, their oldest patient being only thirty months. Speaking of the possible aetiological role of intravenous therapy, they state that such injections have been shown to promote agglutination of blood-platelets, but that experimentally clotting of the blood in the large venous channels will not follow unless the circulation is also slowed. The superior longitudinal sinus was thrombosed in all these patients, although the clot had extended to its tributaries and other sinuses in some. The site of election was its middle three-fifths, where it suddenly widens and its walls contain the lacunar pockets of the arachnoid villi. They suggest that the blood concentrated by diarrhoea and vomiting finds in this part of the sinus just those conditions necessary for a sufficient slowing of the circulation to produce thrombosis, and that the sunken anterior fontanelle may well be an additional retarding factor.

2.—CLINICAL PICTURE

The premonitory symptoms vary with the cause. In the infective class, high swinging temperatures, rigors, and even evidence of infarction of the lung may be added to the pain, tenderness, swelling, and glandular enlargement produced locally by the primary sepsis. In the non-infective class a period of acute gastro-intestinal disturbance will have preceded the actual thrombosis by two or three weeks, and the child will present a picture of severe dehydration and collapse.

(1)—Thrombosis of Superficial Cerebral Veins

Thrombosis of the superficial cerebral veins is usually secondary to clotting of the superior longitudinal sinus, but a generalized purulent leptomeningitis may occasionally be responsible. Diffuse cerebral changes necessarily follow, with focal epilepsy and other signs of destruction of cortex, such as dementia, hemiplegia, hemi-anaesthesia, or hemianopia according to the position of the thrombosed radicles. Blood escapes into the subarachnoid space, or even into the subdural space if the thrombosis is near the junction of the vein with the superior longitudinal sinus. Byers and Hass believe that thrombosis of the superficial cerebral veins is a puzzling, but not uncommon, complication of serious illness in infancy, and because of the sequelae such children are often wrongly assumed to have suffered from some
 17 obscure encephalitis. The cerebrospinal fluid shows variable cellular changes according to the cause, but the presence of erythrocytes or of altered blood from subarachnoid haemorrhage is an important diagnostic point.

(2)—Thrombosis of Superior Longitudinal Sinus

Until recently, any extensive thrombosis of the superior longitudinal sinus was regarded as necessarily fatal, but the work of Byers and

Hass, Bailey and Hass (1937, a and b), and Symonds suggests otherwise. In 1931 Symonds, in describing a condition he called otitic hydrocephalus, recognized that its pathology was obscure but that it must be presumed to be caused either by an excessive secretion of cerebrospinal fluid from the choroid plexus or its defective absorption through the arachnoid villi. In a second paper (1937) he reported five new cases and concluded that infection of the lateral sinus, not necessarily with complete obstruction but with retrograde thrombophlebitis of the superior longitudinal sinus, was the most important aetiological factor. In support, he cited cases of hydrocephalus in which this sinus was proved to be blocked. In one of these (Ellis) the original infection had not been in the middle ear but in the umbilical cord and thence caused multiple venous thromboses. With obstruction of the sinus, the cerebrospinal fluid can no longer escape by the arachnoid villi although it continues to be formed by the choroid plexuses. An increasing amount collects in the ventricles and subarachnoid space, and a communicating hydrocephalus is the result. The symptoms can all be explained in terms of a gradually rising intracranial pressure. If the sutures have not joined, the bones of the vault separate and the head enlarges. In older patients there are severe headache, drowsiness, vomiting, and papilloedema. Palsies of the sixth pair of cranial nerves and extensor plantar responses have been recorded, but the disappearance of these signs with treatment by lumbar puncture suggests that they depend merely on the raised intracranial pressure. The cerebrospinal fluid is otherwise normal in most cases, but sometimes there is a slight pleocytosis.

*Symptoms
of raised
intracranial
pressure*

*Cerebrospinal
fluid*

(3)—Lateral Sinus Thrombosis

Thrombosis of the lateral sinus is not declared by any local sign on physical examination. Nevertheless it may be recognized clinically by the Tobey-Ayer test. This is based upon the rise of the pressure of the cerebrospinal fluid normally following compression of the internal jugular vein. The pressure is measured first with the patient lying comfortably with the head slightly extended and breathing freely. This 'initial pressure' is normally equal to 120 to 140 mm. of fluid in the ordinary left lateral position. The internal jugular vein is next compressed, first on one side and then on the other. With each compression the fluid-level in the manometer normally rises swiftly by at least 100 mm., but if one lateral sinus is obstructed the fluid only moves slowly or not at all. Unfortunately for this test, the size of the lateral sinus normally varies widely. Occasionally it is absent, more often it is an insignificant channel compared with its fellow. In the first case complete obstruction, and in the second a partial mural thrombosis may be wrongly diagnosed. To avoid this difficulty, Frenckner has demonstrated the patency of the sinuses radiographically. The superior longitudinal sinus is injected with a fluid opaque to X-rays, a radiograph being taken at a suitable interval. It is early to say that this method is

*Tobey-Ayer
test*

free from risk, but it appears to distinguish between an anomaly and a thrombosis of the lateral sinus.

(4)—Cavernous Sinus Thrombosis

The classical picture of cavernous sinus thrombosis is seen when its anterior portion is affected. There is extreme proptosis, with oedema of the skin of the eyelids, chemosis, engorgement of the vessels of the conjunctiva and of the retina, papilloedema with widely scattered haemorrhages, and paralyses of the third, fourth, and sixth cranial nerves. If, however, only the posterior part of the sinus is thrombosed, all evidence of interference with the venous drainage of the eye may be absent, the signs being limited to affection of the nerves embedded in the wall of the sinus. In such cases the infection has usually reached the sinus from the pterygoid plexus or as a retrograde extension from the lateral sinus or internal jugular vein by way of the petrosal sinuses. Tonsillar, nasopharyngeal, or otitic symptoms will therefore have preceded the thrombosis. If there is a spread to the opposite side by way of the inter-cavernous sinuses, then all or some of these symptoms may be bilateral.

3.—COURSE AND PROGNOSIS

It might be thought both that the course of the illness was more rapidly deteriorating and that its outlook more hopeless in the septic than in the non-infective group of cases, but it is impossible to make any such generalization. On the one hand, the clotting of a vein from adjacent sepsis does not necessarily imply invasion of the thrombus or of the blood-stream by living organisms; on the other, the non-infective group is composed of young infants already gravely ill at the time of the thrombosis. If a septic case remains untreated, bacterial invasion of the thrombosed vein, purulent liquefaction of the clot, pyaemia, and meningitis will inevitably lead to a fatal termination. Such a sequence, however, is rare to-day, at least in thrombosis of the lateral sinus, in itself by far the commonest example of septic thrombophlebitis. In otitic hydrocephalus, the outlook is good if the pressure of the cerebro-spinal fluid is kept within normal limits by lumbar puncture. The prognosis is far less good in septic thrombophlebitis of the cavernous sinus. The infection nearly always reaches this sinus by way of its tributary veins and is well established in the clot by the time the case comes under observation. Moreover, the pulsations of the internal carotid artery and the great number of tributary channels are factors tending towards the early dissemination of purulent material. Most patients die whatever is done. Thrombosis involving many of the superficial cerebral veins is probably not compatible with life, but lesser degrees may be followed by gradual improvement with such permanent sequels as mental deterioration, epilepsy, or hemiplegia.

Thromboses arising secondarily to diffuse purulent leptomeningitis weigh the balance, already overloaded, against recovery.

4.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of thrombosis of the dural sinuses or superficial cerebral veins has been sufficiently indicated already. *Otitic hydrocephalus* alone needs further discussion. The symptoms and signs of a rising intracranial pressure in otitis media may suggest the more serious intracranial abscess, but the general condition of the patient is distinctive. In otitic hydrocephalus he is in fair health, alert, and interested in his surroundings, particularly after lumbar puncture; in abscess, an enduring physical and mental depression is evidence of a profound general toxæmia. The examination of the fluid is of less help, as a mild localized meningitis related to the original lateral sinus thrombosis may cause a slight pleocytosis in the usually normal fluid of otitic hydrocephalus. Conversely, many cases of well encapsulated deep cerebral abscess may run their course without alteration in the number of cells. If the thrombosis of the superior longitudinal sinus is not secondary to otitis media but to some distant thrombophlebitis, the presence of papilloedema may be taken to indicate an intracranial new growth. The absence of definite localizing signs, the non-progressive course, and the dramatic improvement following the removal of even quite small amounts of cerebrospinal fluid will reveal the true diagnosis.

5.—TREATMENT

In the infective class, the first aim of therapy must be to eradicate any sepsis capable of spreading to the sinuses. Much of this treatment must be operative, the details of which cannot be discussed here, but the sulphanilamide preparations are valuable adjuvants, although it is doubtful if they can replace surgery when purulent foci are already established. In the non-infective class, the control of acute gastroenteritis or at least the extreme degrees of dehydration caused by this disease should be the greatest factor in prophylaxis. Intravenous therapy is probably best avoided in such cases. *Preventive Sulph-anilamide*

A formed thrombus cannot be attacked surgically in any of the intracranial veins or sinuses except the lateral sinus. Even in this situation the wisdom of doing so is doubtful unless the clot is proved to be purulent, in which case the sinus must be drained like any other abscess cavity. Surgery may also help indirectly in the treatment of established cavernous sinus thrombosis, not only in assuring a thorough drainage of the septic process by the track along which it reached the sinus but in placing the sinus at rest by ligature of the carotid artery. A chance is thus given of consolidation of the clot and limitation of the spread of sepsis within it. *Surgical Ligature of internal carotid*

The symptomatic and curative value of repeated lumbar puncture in otitic hydrocephalus has already been mentioned. The effect is usually dramatic and, since Symonds' paper in 1937, this treatment is justified as much theoretically as in practice. The procedure is without danger, provided the fluid is withdrawn slowly and its pressure is never allowed to fall below normal. A manometer is therefore essential, several pressure-readings being taken at intervals after the removal of small amounts of fluid. Puncture is repeated if symptoms return and may have to be performed at gradually increasing intervals of a few days for a few weeks.

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THRUSH

See FUNGOUS DISEASES, Vol. V, p. 465

THYMUS GLAND DISEASES

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1483.] So variable are the size and shape of the thymus at different ages that anatomical descriptions are conflicting, and so scanty are the established facts concerning its function that it is in most instances impossible to correlate the clinical pictures commonly attributed to disease of the thymus with the knowledge of its function obtained from such experimental procedures as its excision and injection of its extracts. Certain syndromes have been attributed to disease of the thymus, mainly on two grounds: (i) that their symptoms are sufficiently often associated with what is interpreted, on radiological or post-mortem evidence, as enlargement of the thymus that a causal relationship may be justifiably assumed; and (ii) that with the shrinkage of the organ, for example as age advances or after radiotherapy, the symptoms disappear.

1.—EMBRYOLOGY AND ANATOMY

The thymus lies in the lower neck and superior mediastinum. It has two lobes bound together by ensheathing fascia. Its immediate anterior *Anatomical relations* are the manubrium sterni, and the sternohyoid and sternothyroid muscles, with pleura overlapping the lower poles; it lies on the trachea and the left innominate and inferior thyroid veins, the

aortic arch, innominate and left common carotid arteries, and the phrenic, vagus, and recurrent laryngeal nerves, and inferiorly it reaches the pericardium. Its blood-supply comes from the internal mammary and the superior and inferior thyroid arteries, and it receives branches from both the vagus and sympathetic nerves.

Its lobes are composed of many lobules or follicles, and in each follicle can be recognized cortex and medulla (see Fig. 2). The cortex

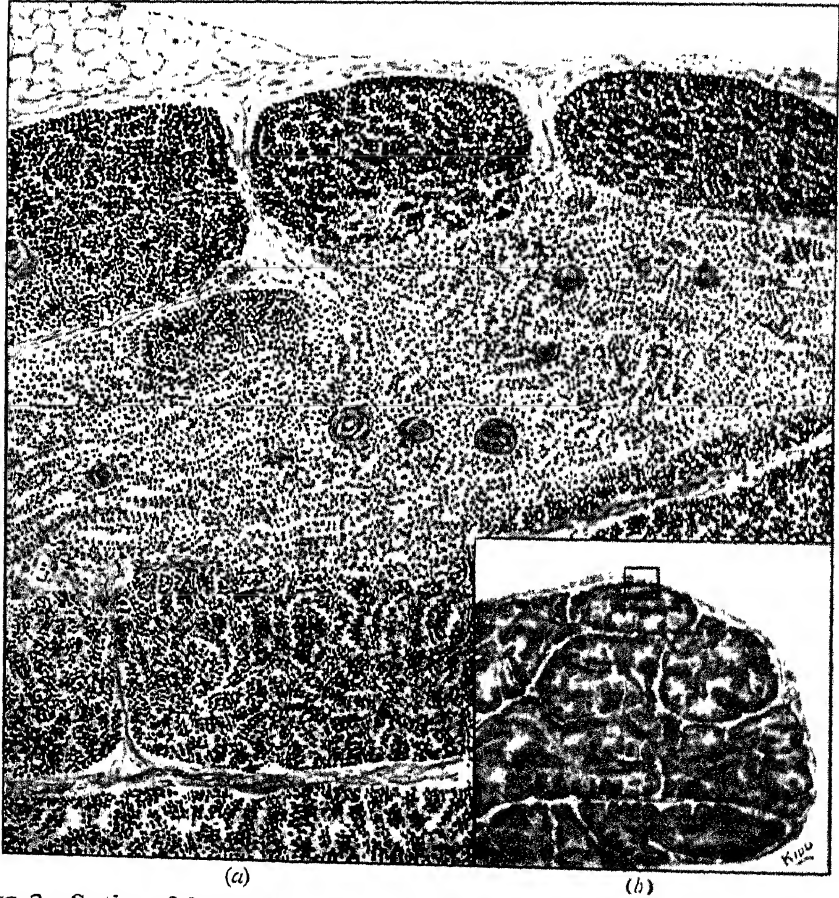


FIG. 2.—Section of thymus gland (*a* $\times 120$, and *b* $\times 4$) showing lobules differentiated into cortex and medulla; the more darkly staining lymphocytes of the cortex and the more lightly staining thymocytes with numerous Hassall's corpuscles can be seen in the medulla; small square indicates the field which is seen enlarged in (*a*)

is made up of compact lymphoid tissue; the medulla contains (i) lymphoid cells in smaller numbers than the cortex, (ii) thymocytes, large cells derived from the original epithelial elements, and (iii) Hassall's corpuscles.

The lobes arise from the ventral diverticulum of the third, sometimes the fourth, branchial cleft. The parathyroids arise from the dorsal

diverticulum of the same clefts; this explains the occasional presence in a case of generalized osteitis fibrosa of a parathyroid tumour not in its expected site, but in the superior mediastinum, in contact with or embedded in the thymus. It is moreover of interest in this connexion that a possible relation of the thymus gland to calcification has been suggested by the work of more than one investigator.

For several reasons the average size of the normal gland at different ages is not established with certainty. The gland rapidly shrinks in starvation and disease so that information derived from necropsies in morbid conditions is not applicable to the healthy gland. It might then be thought that sudden death in health would afford suitable data. But in these cases it is alleged that one of the factors responsible for sudden death is an unusually large thymus, status thymico-lymphaticus. Hence the only cases which can justifiably be used to establish the normal growth and size of the thymus are those in which sudden death has resulted from great violence or extensive injury. Hammar showed that there is a gradual increase in the size of the gland until puberty, followed by a very slow involution, but remnants of thymus may persist even in old age. He gave the following average weights: at birth, 13 grams; at 5 years, 23 grams; at 10 years, 26 grams; at puberty, 37.5 grams; and at 20 years, 25 grams. Similar findings were recorded by Young and Turnbull, who stated that at birth the average weight of the gland is 21 grams; there is a gradual increase to 34 grams at puberty, and then a gradual decline to 15 grams by middle age. Bratton, however, found a rapid increase in size in the first two years of life, followed by a very slight shrinkage until the seventh year, then increase until the twelfth year, after which involution slowly occurred.

*Average
normal size*

*Normal
variations
in size*

2.—PHYSIOLOGY

Although the thymus occurs in all vertebrates, no clue to its function has yet been obtained from its comparative anatomy. It has been variously regarded as (i) a part of the lymphatic system, (ii) a vestigial structure, a view suggested by its epithelial origin and its tendency to lymphoid transformation (compare the vermiform appendix), and (iii) an endocrine gland. Most often it is discussed in the last category.

Attempts to determine the functions of the thymus have followed in the main those methods which have yielded fruitful results in investigating the endocrine glands, namely, (i) removal of the gland at different ages, (ii) administration orally and parenterally of the gland or its extracts, and (iii) correlation of clinical observations with findings at necropsy. Up to the present the results thus obtained have not been sufficiently clean-cut and consistent to correlate the experimental and clinical findings.

*Methods of
determining
function*

Basch first showed that experimental thymectomy produced softening of bones resembling rickets, and Klose and Vogt not only confirmed

*Experimental
thymectomy*

this but reported that thymectomy was followed after a latent period by adiposity and then cachexia which led to death from nutritional disturbances. Park and McClure, from an investigation on dogs, concluded that the thymus is not essential to life in the dog; and its extirpation does not produce detectable alteration in the hair, teeth, contour of the body, muscular development, strength, activity, or intelligence of the experimental animal. Their work suggests that thymectomy probably does not influence growth or development, but the possibility that it may retard development and union of the epiphyses cannot be absolutely excluded. Extirpation of the thymus probably does not induce any alterations in the endocrine organs. Possibly it may be responsible for well marked changes in the organs of internal secretion in the period immediately following thymectomy, which was not covered in the experiments of Park and McClure.

The possibility of damage to the parathyroid glands during extirpation of the thymus as a cause of the bone changes has not been adequately considered but deserves notice because in some animals thymectomy rendered the peripheral nerves more excitable to galvanism, a symptom of tetany.

A possible relation of the thymus to calcification is suggested by two observations on birds. Soli found that after thymectomy pullets temporarily laid eggs without shells, and Riddle showed that pigeons which at necropsy had a defective thymus occasionally had laid eggs deficient in shell.

*Thymus
feeding*

Although Gudernatsch reported a rapid increase in the growth of tadpoles after thymus feeding, he accepted Uhlenmuth's view that this was not a specific glandular effect but the result of the nutritive value of a thymus diet. In 1930 Asher found that the daily administration of an aqueous thymus extract, 'thymocresein', overcame the loss of weight following on a vitamin-free diet, stimulated growth, and increased the size of the gonads.

*Intra-
peritoneal
injection of
thymus
extract in
rats*

The most striking effects on growth in rats was reported by Rowntree and his co-workers who injected intraperitoneally daily for sixteen months into successive generations of rats a thymus extract prepared by Hanson ('karkinolysin', so called because it was intended for the treatment of cancer). In the first generation the treated test animals were heavier, bred more frequently, and had larger litters of heavier average weight per rat. Little of note appeared in the second generation in the first six litters cast, but in the later litters (the seventh to the eleventh) precocity appeared. In the tenth and eleventh litters the animals were larger than normal, teeth erupted on the second day, and the eyes opened on the tenth day. In the animals of the third to seventh (F2 to F6) generations, striking and accruing precocity, and acceleration in growth and development were noted in the offspring of each succeeding generation under treatment. Similar effects were not observed from thymus feeding. Investigations on the blood made throughout the series showed no change in the haemoglobin or red

or white cell counts, but there were significant changes in the calcium and phosphorus contents of the plasma. In contrast to the normal values of 9 to 11 mgm. of calcium and 3 to 4 mgm. of phosphorus per 100 c.c., the second to fourth generations had 11.4 to 12.3 mgm. (average 12.3 mgm.) of calcium and 4.0 to 7.5 mgm. (average 6.1 mgm.) of phosphorus respectively. Radiographs of the test animals showed (i) an increase in the size of bones in all dimensions, especially the length of the diaphyses, (ii) earlier appearance of centres of ossification in the epiphyses, and (iii) earlier calcification and union of diaphyses and epiphyses. These investigators found that small doses of the extract had no effect on the heart but that with large doses the blood-pressure fell and death occurred from complete heart-block, a fact not yet capable of correlation with the sudden death of so-called status thymicolymphaticus. Their results were summarized thus: 'The continuous administration of thymus extract (Hanson) results in marked precocity in the offspring of treated parents after the second generation. The young show increased growth and development, small adrenal glands and lymphatic hyperplasia, specially marked in the glandular structures of the intestine, but they show no susceptibility to sudden death from fright, the use of the hypodermic needle, immersion in cold water, or from operation or anaesthesia.'

Lee and Ayer obtained similar results by injecting glutathione, which, they suggest, is the effective principle in the extract used by Rowntree, Clark, and Hanson. Marangoni obtained similar acceleration of growth in successive generations of yeast-fed guinea-pigs; yeast contains glutathione.

Unlike hyperpituitary rats, these hyperthymic rats do not become giants because their rapid rate of growth decreases from the second month. Thymectomy, however, in four successive generations of experimental animals has given rise to retardation in the rate of growth and to a slight delay in the rate of development (Einhorn and Rowntree).

3.—RELATION OF THYMUS TO ENDOCRINE SYSTEM

In an endeavour to ascertain the relation of the thymus to the endocrine glands, extensive experimental and clinical observations have been made, but the recorded changes are confusing and often contradictory. The most significant findings may be summarized as follows.

Marine, Manley, and Baumann showed that thyroidectomy hastened *Thyroid* the physiological involution of the thymus. Aschoff described hypertrophy of the thyroid after thymectomy. Scott Williamson and Pearse regarded the thymus as a lymph reservoir for the thyroid. Clinical observations show that 'thymic hyperplasia is constant in toxic goitre in patients under 40 and in half the patients over that age' (Blackford and Freligh). In infantile myxoedema the thymus is atrophied.

- Gonads* Though many negative results have been recorded, the weight of evidence, both experimental and clinical, suggests that gonadectomy delays thymic involution in both males and females. In the rabbit it has been shown (Lucien and Parisot) that the onset of thymic involution coincides with spermatogenesis.
- Pituitary* Cushing found persistence of the thymus in dystrophia adiposogenitalis, and that experimental hypophysectomy was followed by thymic hyperplasia. In hyperpituitary gigantism and acromegaly the thymus is said to be enlarged.
- Adrenals* Marine and his co-workers found that adrenalectomy not only delays involution of the thymus and lymphoid tissues but actually causes their regeneration. Conversely, thymectomy has been followed by adrenal cortical hyperplasia. In Addison's disease there is hyperplasia of the thymus. For the clinical syndromes attributed to thymic hyperplasia and said to benefit by adrenal cortical extracts, see page 34.
- Conclusions* These observations suggest that (i) although disturbance of the thyroid, gonads, pituitary, and adrenals leads to fairly constant and well defined changes in the thymus, experimental thymectomy is followed by inconstant and indefinite changes in the endocrine glands; (ii) thymic changes in endocrine disturbances are part of the general growth changes (skeletal and sexual) which follow these disturbances and are not specific to the thymus; and (iii) the thymic hyperplasia associated with thyrotoxic states is not an indication of a reciprocal endocrine relation between thyroid and thymus but simply a part of the general lymphoid hyperplasia which accompanies thyrotoxicosis.

4.—DISEASES OF THE THYMUS GLAND

Interest in disease of the thymus gland has centred not in the well defined morbid conditions, such as infections, to which it is rarely subject, but in a group of symptoms varying from breath-holding spells to sudden death, which has been attributed to persistence or hyperplasia of the thymus—the so-called 'status thymico-lymphaticus'.

Congenital absence Congenital absence has been recorded without any other malformations, but it is not uncommon in anencephaly and is occasionally noted in the still-born. Accessory thymus nodules may be found in the thyroid region and the superior mediastinum and very rarely as subcutaneous tumours in the neck. It is suggested that some deep-seated carcinomas of the neck may originate in accessory thymic tissue.

Accessory thymus nodules

Atrophy Atrophy of the gland occurs in malnutrition from any cause, e.g. starvation and prolonged infection. It differs from the normal involution of the thymus in showing fibrosis without fat formation; involution is accompanied by a progressive replacement of the parenchyma by fatty tissue.

Petechial haemorrhages of no clinical significance occur in asphyxia, whatever the cause, and haemorrhagic blood diseases. Larger extra-

sations may occur in acute infections and have been described in syphilis of the new-born (Friedleben).

Acute thymitis is extremely rare as a primary condition, though abscesses have been found in pyaemic states and extending from neighbouring viscera. Swelling of the thymus has been reported in mumps and other acute infective diseases. *Acute thymitis*

Demme reported a case of primary tuberculous thymitis, no other organ of the body being involved at necropsy. Several observers have found the thymus to be rarely the seat of tubercles in generalized tuberculosis of childhood. *Tuberculosis*

In congenital syphilis multiple small softened areas, the so-called Dubois' abscesses, were at one time regarded as resulting from colliquative necrosis of Hassall's corpuscles; they are now accepted as softened caseous gummata and contain *Spirochaeta pallida* in large numbers. The treponema is found in the thymus in the vast majority of cases of congenital syphilis even in the absence of any histological change. The occasionally persistent thymus in adults with generalized syphilitic lymphadenitis may show miliary gummata. *Syphilis Dubois' abscesses*

Diseases of the blood-forming tissues

In diseases associated with generalized lymphoid hyperplasia—leukaemias, chloroma, the lymphoblastomas, and leucosarcomas—the thymus may participate. In rare cases it may be the primary seat of the morbid change.

Myasthenia gravis

In about 20 per cent of cases of myasthenia gravis the thymus is abnormal. Simple hyperplasia, hyperplasia with degenerative cystic changes, lymphosarcomas, endotheliomas, and carcinomas have all been described, but no tenable hypothesis of the significance of these changes in myasthenia gravis is forthcoming. The relation of the thymic changes to the clumps of mononuclear cells—lymphorrhages—found in the muscles and occasionally in the nervous system in myasthenia gravis is unknown though they are certainly not secondary deposits from a primary thymic neoplasm as Weigert suggested. The occurrence of lymphorrhages and myasthenic reactions in patients suffering from toxic goitre (Dudgeon and Urquhart) recalls the association of thyrotoxicosis and thymic hyperplasia.

Tumours

Benign tumours are extremely rare, though degenerative cysts and cysts derived from epithelial rests of the embryonic thymus have been described. Teratomas, including dermoid cysts lying in the superior mediastinum, are probably not of thymic origin. *Benign*

Malignant tumours are also rare. Most have the histological appearance of round-celled sarcomas but their origin, whether from mesoblast or entoderm, is obscure. It is doubtful if histological appearances justify the more detailed differentiation attempted by some investigators. But sarcoma from the fibrous tissue, lymphosarcoma from the lympho- *Malignant*

'Thymoma'

cytic tissue, perithelioma from the blood-vessels, and carcinoma from the reticulum-cells and Hassall's corpuscles have all been described. Many authors use the term 'thymoma' to describe these tumours arising in the thymus gland. There is little doubt that many of the tumours described as thymogenic originate in the mediastinal lymph glands.

Clinical picture

Most cases of 'thymoma' show their presence by evidence of pressure on neighbouring structures, e.g. trachea, veins, and nerves, the resulting clinical picture being the sum of these pressure effects. The presence of a superior mediastinal mass can be shown by X-rays (see Plate III, B). Rarely secondary deposits occur in the lymphatic glands of the neck.

Endocrine disturbances

The occurrence of endocrine disturbance in tumours of the thymus gland has been noted by Leyton, Turnbull, and Bratton who observed clinical changes apparently identical with those now described as due to pituitary basophilism (Cushing's syndrome) in two males aged 11 and 31 years. In both cases, necropsy revealed that 'a small-celled, medullary carcinoma of the thymus, was associated with great hypertrophy of the cortex of the suprarenal bodies, functional hypertrophy of the thyroid gland, infiltration of the medulla of the suprarenal bodies with lymphocytes and plasma cells, and fatty infiltration of the centres of the hepatic lobules'. Stress should be laid on the greatly hypertrophied adrenal cortex, for this alone may give rise to a syndrome clinically indistinguishable from that of pituitary basophilism. Walters, Wilder, and Kepler described a thymic tumour, about 5 cm. in diameter, in a patient showing the adrenal cortical syndrome, though they gave no details of its structure. Duguid and Kennedy described enlargement of the adrenals, glycosuria, and a colloid goitre accompanying a small-celled medullary carcinoma of the thymus in a woman aged 64 years. Before a thymus tumour can be regarded as a primary cause of adrenal cortical hypertrophy further evidence of the association is desirable.

5.—STATUS THYMICO-LYMPHATICUS

(*Synonym.*—Lymphatism)

Few more controversial problems exist in medicine than 'status thymico-lymphaticus'.

(1)—Thymic Death

History

In the vast majority of cases of sudden death necropsy reveals a condition demonstrably incompatible with life. But occasionally an apparently healthy child or young adult dies suddenly from a trivial injury, or without ascertainable cause, and the most searching necropsy fails to reveal any gross morbid changes in the vital organs. Such minor operations as the extraction of a tooth, opening an abscess, circumcision, the prick of a needle for a hypodermic injection, the shock of sudden immersion in cold water, a mild electric shock, or a slight scald or burn, all of which can be tolerated unflinchingly by the overwhelming

mass of human beings, have to a few spelled death. The reason is still obscure, but the contribution to its solution made by Paltauf in 1889 forms the basis of the conception of status thymico-lymphaticus. Briefly, he maintained that in these cases of otherwise inexplicable sudden death there was found at necropsy, with significant constancy, an enlarged thymus. He was not primarily concerned with how the enlarged thymus produced its lethal effects, though he supported Friedleben in rejecting the view that it was due to obstructed respiration caused by the mechanical pressure of the thymus on the trachea. He suggested that the victims of this sudden death from trivial causes had a different 'body make-up' from the normal and that one of its manifestations was an enlarged thymus. Accompanying signs were hyperplasia of other lymphatic tissues—the lymph glands, tonsils, salivary glands, and agminated follicles of the small and large intestines; a flabby fat overgrowth of the body and hypoplasia of the heart and blood-vessels; a hyperplastic bone marrow with replacement of the yellow by red marrow; and adrenal atrophy. To avert this tragic death, the habitus must be recognizable during life and its less serious manifestations observed and treated. To these latter the terms 'lymphatism' and 'thymic syndromes' have been applied; the fatal cases are referred to as 'thymic death'. *Paltauf's hypothesis* *'Lymphatism'*

Paltauf's papers were followed by many records of sudden death from trivial causes in which the thymus was described as enlarged or persistent. In recent years, however, Paltauf's papers and those subsequently published have been subjected to critical analysis, and emphasis has been laid on the fact that these papers appeared before the establishment of such fundamental data as the normal variations of the thymus in respect of age, sex, body-weight, and height, and the effects of acute illness, wasting diseases, and the endocrine disturbances already mentioned. It is to Hammar's monumental work on the thymus that we owe the more important data. Later Greenwood and Woods, in a statistical analysis based on Hammar's and their own researches, undermined the whole conception of status thymico-lymphaticus as the cause of sudden death. In a joint study with Turnbull they analysed the data of some 3,500 necropsies on persons up to the age of 16 and, comparing their results with Hammar's, concluded that 'at ages between 1 and 16 years the normal weight of the thymus has been well determined'. They were unable in the absence of more precise knowledge to answer with certainty the fundamental question within what limits the weight of the thymus of a child of known age, height, and body-weight could be described as normal. They obtained, however, a crude approximation to the frequency with which defined deviations from the 'expected' value were likely to occur; for example they found that 'for males, a child aged 9 weeks, weighing 3.9 kilos and measuring 54 cm. would have on the average a thymus weighing 16 gm., and that only once in a thousand would we expect to have a greater weight than 40 gm. A boy aged 7 years, weighing 19 kilos and measuring *Criticisms of Paltauf's hypothesis* *Hammar's work*

109 cm. might be expected to have a thymus weighing 26 gm., and only once in a thousand trials should we expect a thymus of 55 gm. A thymus of 40 gm. or more would be expected in 7 or 8 per cent of children of this age and dimensions. In girls, taking precisely the same ages and dimensions (these happen to be the approximate means for the boys) we should expect thymus weights of 13.7 and 24.6 gm. respectively, and one in a thousand of each class to exceed 25.6 and 48.8 gm. respectively.'

With these rough indications of the limits between which a thymus might reasonably be regarded as normal, they analysed the records of 21 cases (17 male and 4 female) in which the weight of the thymus exceeded the predicted weight by an amount which might occur in about 1 in 44 cases taken at random and was therefore well outside what might be regarded as normal limits. They found that in every instance the cause of death was adequately determined. They concluded: 'If the criterion be mere weight of the thymus, then status lymphaticus, status thymico-lymphaticus, and status thymicus are mere verbalisms. Diagnoses established wholly or mainly upon an alleged abnormality of weight of the thymus have no more value than affirmative evidence in cases of witchcraft. Since it can seldom be possible for a certifying practitioner to have *more* knowledge of the thymus than he will acquire by putting it in the scale pan—some may even content themselves with a visual appreciation—it follows that, for practical purposes, the diagnosis ought to be abandoned. In cases of sudden death, the old inquest verdict of "Died by the visitation of God" is at least as scientific as and more modest than "Status thymicus" or "lymphaticus"; "Cause unknown" is to be preferred to either.' Greenwood (1930) referred to status thymico-lymphaticus as a 'mere farrago of random assertion and debased tradition'.

*Results of
special
committee's
investigations*

*Deaths due to
anaesthesia
or shock*

*Death due to
other causes*

A joint committee of the Medical Research Council and the Pathological Society of Great Britain and Ireland was set up in January 1926 to collect on a large scale information on the weights and measurements of the thymus and to investigate closely the precise cause of death in persons dying suddenly from unexplained or trivial causes who at necropsy were found to have an enlarged thymus. This investigation analysed twenty-three cases in which death was attributed to anaesthetics or shock, in only four of which was the thymus considered abnormally large for the age; in one a major operation had been performed, and in another purulent bronchitis with dilatation of the right ventricle and hypertrophy of the thymus were noted at necropsy.

The committee found thymic changes in two of the cases not attributable to shock or anaesthesia; the first, a five-year-old male, died after tonsillectomy under general anaesthesia; at necropsy blood was found in the bronchioles and alveoli of the lungs and in the stomach. This boy's thymus weighed 99.2 grams, thus exceeding the normal average for his age-group by more than five times the standard deviation, and was said to have encircled the trachea, but an adequate

cause of death was asphyxia from the aspirated blood. The thymus of the second case, a female child aged two, weighed 14.2 grams, thus exceeding half the value of the normal average of this age-group. She was admitted to hospital with marked laryngeal stridor; immediate tracheotomy without an anaesthetic was performed and she died. There was not any evidence at necropsy of diphtheria or laryngeal obstruction and, although death was attributed clinically to thymic asthma and status lymphaticus, a relatively small thymus had been found.

This joint committee concluded that 'the facts elicited in the present inquiry are in harmony with those of Hammar (1926 and 1929) and Greenwood and Woods (1927), in affording no evidence that so-called "status thymico-lymphaticus" has any existence as a pathological entity'. Hammar believed that in those whose death cannot be explained by obvious morbid changes there might be a disturbed endocrine balance, of which changes in the histological structure of the thymus are a part. But these stigmata would have a statistical significance only and be extremely difficult to demonstrate even by an expert in histological technique.

*Committee's
conclusions*

Greenwood in 1930, assisted by further observations on the weight of the thymus, examined Hammar's further data arithmetically. He formed two groups, (i) in which an adequate cause of death was found, and (ii) in which death occurred from some trivial or non-demonstrable cause; he then examined the structural character of the thymus in these groups to discover whether they were thereby significantly differentiated.

The numerical characters which Hammar used were: (i) the gross weight of the thymus in grams, (ii) the ratio of cortex to medulla, (iii) the ratio of the number of Hassall bodies with diameters from 26 to 50μ to the number with diameters from 10 to 25μ , and (iv) the ratio of the number of Hassall bodies with diameters 51 to 100μ to that of those with diameters 26 to 50μ . Hammar regarded (iii) and (iv) as indices of progressive or regressive changes in the thymus. Greenwood investigated whether these groups could be differentiated not only by differences in mean values for Hammar's four indices but also by greater variability around the mean. These two criteria are both clinically and biologically significant. If there are significant differences in the size of the thymus in the two groups, then the group differentiation would be of value for, and applicable to, individual cases. All reliable data tend to support the view that such differences between the means of the two groups do not exist and are therefore not of any value for individual differentiation. If, however, there are in the two groups significant differences of variation around the mean, it merely implies that the group showing the more marked variation is less true to type and less stable than the normal group. It does not imply that the criterion is of any special value in differentiating the two groups. A careful study of Hammar's data shows that there is this greater variability around the mean in the 'sudden death group', a fact which

*The Hassall
ratios*

Greenwood's analysis confirms. The conclusion is therefore justified that 'those who die suddenly are likely to have heavier thymuses than normal persons, but they are also likely to have lighter thymuses than others'.

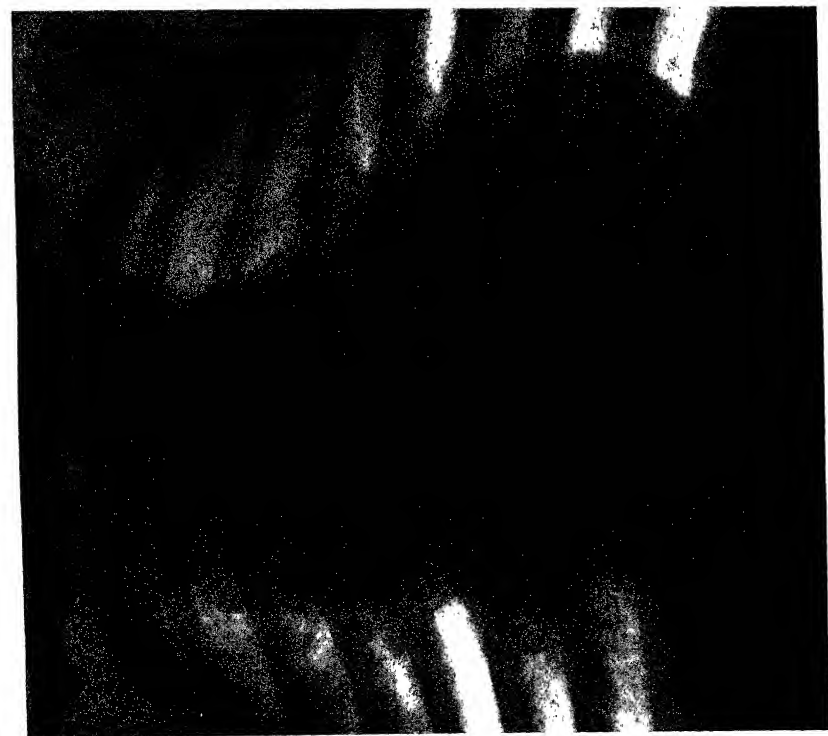
In the ratio of cortex to medulla there appears to be a difference in the mean values of the two groups, but it tends to disappear when the data are corrected for age, and there is no appreciable difference in the variabilities of the index in these two groups. The first Hassall ratio, i.e. the ratio of the number of Hassall bodies with diameters from 26 to 50 μ to the number with diameters from 10 to 25 μ , shows differentiation of both means and variabilities, there being no indication of a sufficiently strict association between age and ratio for age corrections to alter this conclusion. The second Hassall ratio, i.e. the ratio of the number of Hassall bodies with diameters from 51 to 100 μ to that of those with diameters from 26 to 50 μ , shows no differentiation, either in mean or variability.

A careful enumeration of the Hassall bodies might therefore help in group differentiation but as an individual criterion is useless. To quote Greenwood: 'The suggestion is that the thymus, if examined as few men are likely to examine it, might afford differentiae of the groups which interest us, so that, almost hidden by the masses of nonsense and bad observation which form the bulk of the literature of status thymico-lymphaticus, a little truth may be discerned. What has not been shown or even made faintly probable is that an equally painstaking study of other organs or functions (bodily or psychic) would not have revealed at least as clear-cut group differentiae.'

The available evidence then affords no justification for regarding the thymus either as primarily responsible for these unexplained cases of sudden death or as an index of these bodily disturbances which accompany this tendency. The greater variability in the size of the thymus indicates solely the greater instability of this group. The term 'status thymico-lymphaticus' is, on the present evidence, a meaningless term giving an air of profundity to what is a confession of ignorance, for it can mean only that 'this person has died suddenly from an unexplained or trivial cause'.

(2)—Thymic Syndromes

So long as the conception of 'thymic death' received general support it was natural that efforts should be made to recognize the predisposition during life. The rather plump pasty child, sluggish both intellectually and physically, with enlarged tonsils and adenoids and a few enlarged superficial lymphatic glands, and developing rather late sexually was regarded, without any supporting evidence, as especially prone to thymic death. It might have been anticipated that as these children were not good average specimens they would be less likely to resist the ordinary stresses of life. Apart from this supposed predisposition to 'thymic death' various clinical syndromes in infancy and childhood



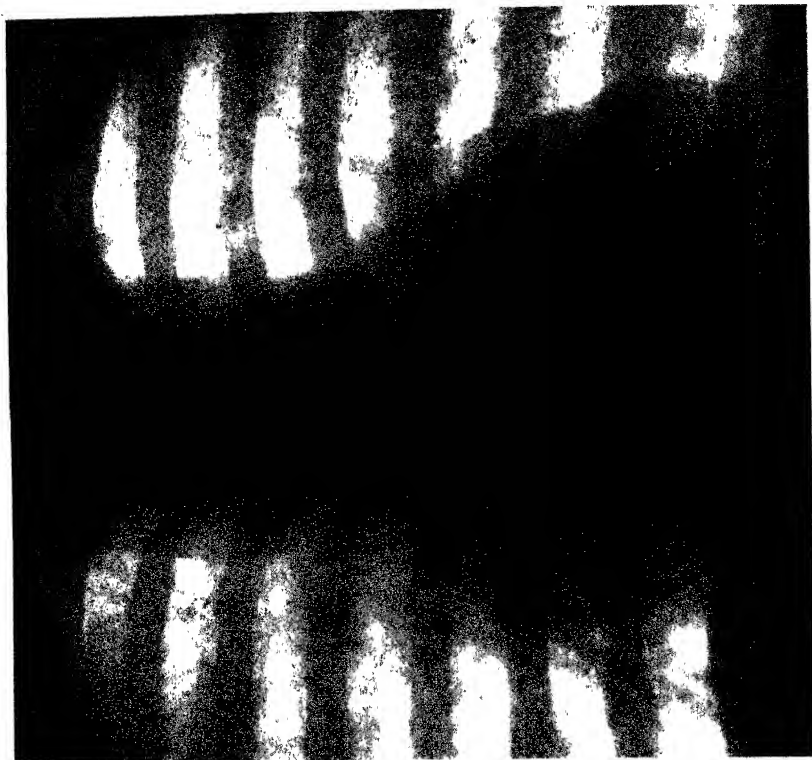
A

- A. Radiograph of male, aged 1 year 3 months, showing persistent thymus; the child was pale and had a paroxysmal cough.
 B. Same child, aged 2 years 9 months; no X-ray treatment had been given to the gland

B



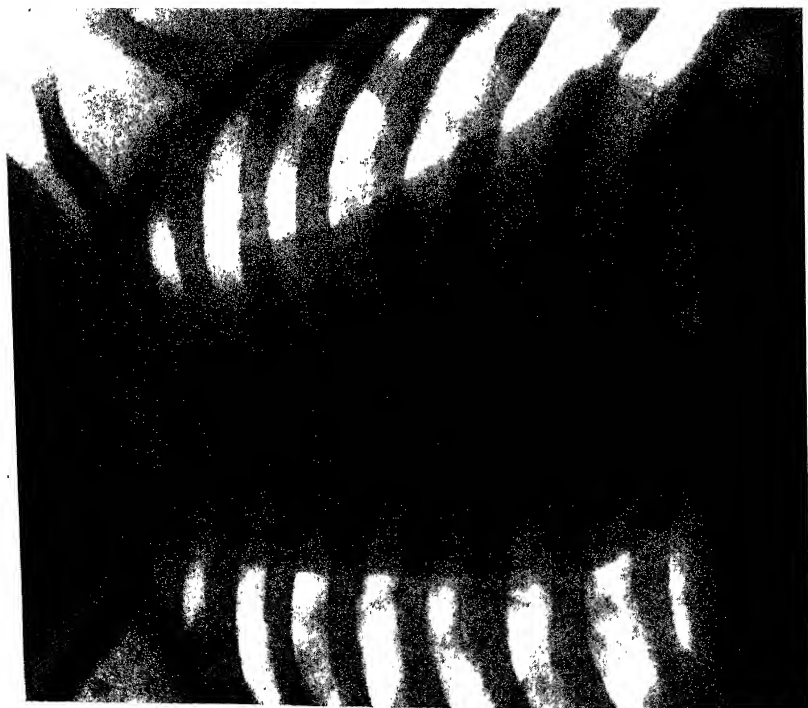
PLATE I



B

A. Radiograph of maxilla of a patient with severe periodontitis, showing advanced resorption of alveolar bone and root resorption.
B. Same patient 2 years' months after X-ray treatment.

PLATE II



A

have been ascribed to thymic hyperplasia or persistence. In these, certain symptoms are alleged to be associated with radiologically demonstrable enlargement of the thymus and to disappear when the gland shrinks as a result of age changes, radiotherapy, or medicinal treatment.

Among the described syndromes are the following: 'During a paroxysm of crying occasioned by an injury or an attack of temper, the child holds its breath, becomes cyanotic and usually falls to the ground. The suffocative attack is at times accompanied by a transient loss of consciousness and may be followed by a period of listlessness, semi-stupor and pallor of some minutes' duration. The attacks may be infrequent, i.e. once a month or they may occur several times in one day' (Morgan, Rolph, and Brown). This description is that of an epileptiform seizure and it is known that crying in children and coughing in adults occasionally give rise to similar attacks even in the absence of demonstrable thymic enlargement. They have then been attributed to disturbances of cerebral circulation, either from venous congestion or from reflexes analogous to the carotid sinus reflex, with resulting slowing of the heart and fall in blood-pressure. The relation of these attacks to thymic enlargement is based on the alleged striking effects of treatment. In one series of twenty-nine cases, twenty-seven were said to be free from attacks after two to three treatments.

Breath-holding spasms

The child is subject to sudden fainting spells, being blanched and limp, with shallow respiration and almost imperceptible pulse. During feeding the child chokes and goes blue, 'as if the food had gone the wrong way'. Cyanosis is often accompanied by choking attacks, but not crying. Sometimes it is said to date from birth and thymic enlargement is held responsible for certain cases of asphyxia neonatorum.

Syncope

Stridor, which is most marked during inspiration and may be present only with catarrhal infections of the upper respiratory tract, is said to occur. Moncrieff suggested that an enlarged thymus is commonly found with congenital laryngeal stridor. Even noisy nasal breathing has been brought within the group of thymic syndromes. Attacks of paroxysmal inspiratory dyspnoea have been recorded and given the eponyms 'Millar's asthma' after John Millar, who in 1769 described afresh what appears to have been laryngismus stridulus, and 'Kopp's asthma' after Kopp, who ascribed the attacks to mechanical pressure of the enlarged gland. Rapid panting respiration is stated to occur in some instances. A persistent chronic hoarse cough is said to be evidence of thymic disturbance when no other cause is demonstrable. Radiotherapy to the thymus is beneficial (see Plates I and II). Head retraction may accompany any of the above symptoms or occur independently. Such nervous disturbances as excessive crying (without fits), restlessness, and insomnia are among the supposed manifestations. Eczema is found in one-fifth of all cases, whatever their type.

Stridor

Cough

Head retraction

Systemic disturbances

Even amongst the most strenuous protagonists of the thymic syndromes,

controversy exists on the mode of production of symptoms. Some ascribe the symptoms to disturbance of an internal secretion of the thymus and support their view by insisting on (i) the associated generalized hyperplasia of lymphoid tissue, (ii) the improvement which follows irradiation of a gland of normal size, (iii) the frequency of associated eczema, and (iv) the latent period between thymectomy and clinical improvement. Others ascribe the symptoms to the mechanical pressure of the enlarged thymus on neighbouring structures, such as on the trachea causing stridor and cough, on the vagi causing syncope, and on the veins causing cyanosis. It is difficult to visualize circumstances in which the gland could enlarge and exert pressure sufficient to cause gross symptoms, though this possibility could not be excluded when the thymus is drawn up into the superior thoracic outlet, the neck being retroflexed. Recent attempts to correlate anaphylactic and allergic phenomena with thymic enlargement are not convincing (Waldbott and Anthony).

6.—THYMIC HYPERPLASIA

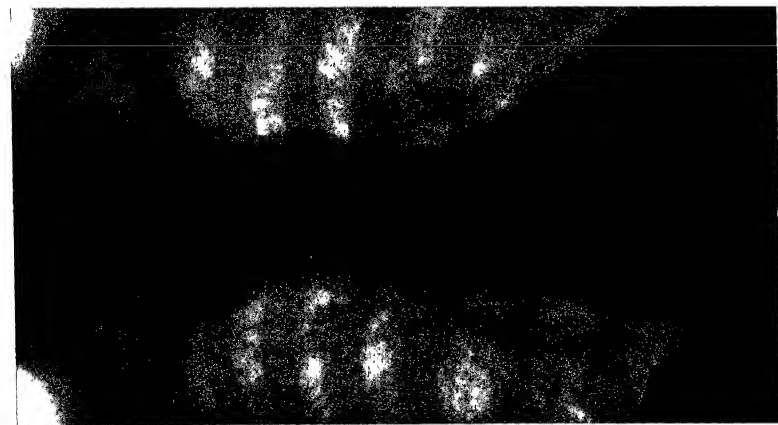
(1)—Diagnosis

The diagnosis of thymic enlargement is made by physical and by radiological examination. Light percussion reveals an area of dullness on either side of the sternum, more marked to the right, which may disappear when the head is flexed. Rehn described the tumour as appearing on expiration in the suprasternal notch, where occasionally it can be palpated. 'A sustained posture with the head held slightly forward, the shoulders slightly raised, the chest slightly expanded, and almost entire abdominal breathing', is described in many instances.

The radiological findings are confusing. Characteristically there is in the superior mediastinum a wide transverse, almost symmetrical, shadow which merges with the heart shadow. This shadow is said to enlarge during systole, expiration, and on crying; and to diminish in diastole, inspiration, and at rest. The appearances are not easily distinguishable from other morbid changes, especially enlarged lymphatic glands, dilated auricles, coarctation of the aorta, congenital malformations of the conus arteriosus, thoracic goitres, and aortic aneurysms (see Plate III, A and C). Even lateral views and fluoroscopic screening may not suffice to differentiate these conditions.

(2)—Treatment

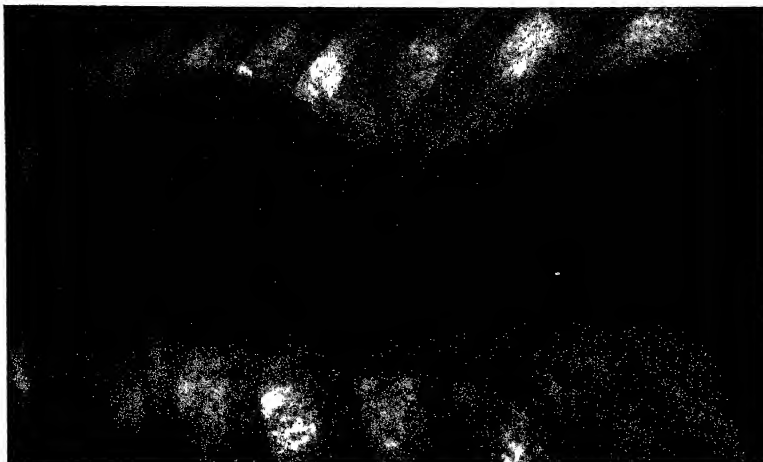
There are many difficulties in accepting a causal connexion between thymic enlargement and the various symptoms described. As, however, the symptoms are often alarming and fail to respond to other methods of treatment, the absence of certain proof of a causal relation between them and enlargement of the thymus is scant justification for withholding from an afflicted infant a form of treatment which some observers believe to be not only beneficial but in many instances life-saving.



A



B



C

Radiographs showing superior mediastinal shadow: A, due to retrosternal goitre; B, shadow proved at necropsy to be due to a malignant thymoma; C, shadow due to an aortic aneurysm

PLATE III

Marine's finding that adrenalectomy not only delayed involution of the thymus and lymphoid tissues but actually caused their regeneration led to Kemp's hypothesis that the cause of thymic syndromes is an acute exacerbation of a temporary cortico-adrenal insufficiency and to his treatment of these syndromes with adrenal cortical extracts. No decisive results have been recorded.

Both X-rays and radium have been used in treatment. The dose of X-rays varies with the age of the child. The technique used by Morgan *et al.* is to give a dose of 20 to 25 milliamperere minutes, using approximately 90 kilovolts with a target skin distance of 10 inches and a filter of 4 mm. of aluminium. This is repeated in a week's time. If symptoms improve, a fortnight's interval is followed by two or more treatments a week apart, making four treatments in six weeks. If there are recurrences, further courses of treatment are given.

For young babies a 'radium-bib' overcomes the difficulties of radiotherapy and offers the advantages of home treatment and more effective application. The bib is made 'with 40 mgm. of radium element on a plaque 3 × 2 inches filtered with 0.5 mm. of lead. It is tied on with straps round the neck and under the arms so as to irradiate the whole of the thymic area. It is applied for 16 hours' (Shires).

Thymectomy, though occasionally undertaken for the removal of tumours of the thymus and the enlarged thymus which accompanies thyrotoxicosis, has rarely been carried out for thymic syndromes.

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THYROID GLAND DISEASES

See GOITRE AND OTHER DISEASES OF THE THYROID GLAND,
Vol. V, p. 599

TICS

See NEURALGIA, GLOSSOPHARYNGEAL AND TRIGEMINAL, Vol. IX, p. 176; PSYCHIATRY OF CHILDREN, Vol. X, p. 207; *and* PSYCHONEUROSES AND PSYCHOTHERAPY, Vol. X, p. 247

TICKS

See ARTHROPODS AND DISEASE, Vol. II, p. 134; *and* BITES AND STINGS, Vol. II, p. 347

TINEA

See FUNGOUS DISEASES, Vol. V, p. 448

TOBACCO BY-EFFECTS

See ANGINA PECTORIS, Vol. I, p. 561; ARRHYTHMIA, Vol. II, p. 20; BLINDNESS, Vol. II, p. 452; HYPERCHLORHYDRIA, Vol. V, p. 16; PEPTIC ULCER, Vol. IX, p. 506; *and* TOXICOLOGY, p. 101

TONSILS DISEASES

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Reference may also be made to the following titles:

NOSE AND NASOPHARYNX PHARYNX DISEASES
DISEASES

1.—ACUTE TONSILLITIS

1484.] Acute tonsillitis is classified as catarrhal, lacunar, or parenchymatous according to its degree of severity. In the common lacunar form, often called follicular, the crypts become filled with desquamated epithelium, pus cells, and organisms forming white or grey dots at the mouths. In the parenchymatous form the whole tonsil and the adjacent pharynx become swollen and infiltrated, and an abscess may form in the substance of the tonsil.

The disease usually occurs in young adults and sometimes in children. In children it may precede an attack of acute rheumatism, so that removal of the tonsils slightly diminishes the incidence of primary attacks of rheumatic infection, but the operation has no influence in preventing recurrent rheumatic attacks nor does it influence the incidence of endocarditis. (See also HEART DISEASES: RHEUMATIC HEART DISEASE IN CHILDREN, Vol. VI, p. 253; and RHEUMATIC INFECTION, ACUTE, Vol. X, p. 641.)

Acute inflammation is particularly liable to occur in the remnants of tonsils which have been partially removed, and in tonsils which are

the seat of chronic inflammation or suppuration. The specific fevers, especially scarlet fever, often begin with an acute attack of parenchymatous tonsillitis.

The commonest causal organism by far is the *Streptococcus pyogenes*, *Causal organisms* but varieties of pneumococci and staphylococci are also found either pure or in mixed infections. In the epidemic streptococcal form the contagion may be carried by milk.

The initial symptoms are malaise and anorexia sometimes with a chill or even a definite rigor. The temperature rises to 102° or 104° F. with corresponding increase in the rate of the pulse, which is full and bounding. There is pain in the throat, radiating to the ears, and increasing difficulty in swallowing with much salivation. *Signs and symptoms*

Acute tonsillitis, which usually lasts from four to eight days, must be distinguished from diphtheria and from Vincent's angina by bacteriological examination. Mild cases must be distinguished from secondary syphilis. In the faucial type of glandular fever which resembles severe tonsillitis, the cervical glands enlarge, there is both a relative and absolute lymphocytosis, and the spleen may be enlarged. The illness may last several weeks but the prognosis is good. *Diagnosis*

In acute tonsillitis aspirin is useful to relieve the pain, or a mixture containing sodium salicylate may be given. It is usual also to prescribe a purge at the beginning of the illness. As the causal organism is the *Streptococcus pyogenes*, it has become customary to prescribe sulph-anilamide. *Treatment: drugs*

Locally a paint containing 2 per cent each of benzamine hydrochloride and formalin in glycerin is useful or in very severe infections with much exudation the throat may be sprayed with eusol. Gargles are useless and increase the pain but a compress, either hot or cold as the patient finds the more suitable, often gives relief. *Local applications*

Junket, ice-cream, custard, and thick soups are easily swallowed. The dysphagia may be relieved by an attendant standing behind the patient with the palms applied behind and below the angle of the jaw on either side. Firm pressure is made just as the patient swallows. *Food and feeding*

If the disease is recurrent, after eliminating such causes as dental sepsis or external sources of infection, the tonsils should be removed (see p. 43), but not until after an interval of at least six weeks. *Operation for recurrences*

2.—QUINSY

1485.] The formation of a peritonsillar abscess or quinsy, which is usually unilateral, is shown by increasing oedema of the uvula and the appearance of a tense swelling on one side of the soft palate, which bulges downwards and forwards.

The abscess should not be allowed to burst through the soft palate or into the tonsillar fossa, but should be opened with sinus forceps at its most prominent point after painting with 10 per cent cocaine. A yellow *Choice of site for opening*

spot often indicates the point at which the pus may be most easily reached but, if this is not obvious, the centre of a line between the base of the uvula and the upper wisdom tooth may be chosen. A peritonsillar abscess may occasionally be opened through the supratonsillar fossa.

Quinsy behind lower half of tonsil

Much less commonly a quinsy may be present behind the lower half of the tonsil. In this event there is some danger that the pus may track along the carotid sheath if the opening for drainage is not placed suitably. The best treatment is to remove the tonsil; this gives perfect

Haemorrhage as sequel

drainage, and there is little bleeding. A rare but grave complication of quinsy is haemorrhage from erosion of one of the large vessels in the immediate neighbourhood.

3.—CHRONIC TONSILLITIS

Enlargement of tonsils

1486.] Enlargement or hypertrophy of the tonsils is sometimes regarded as synonymous with chronic inflammation, but in fact size is no criterion of this and in many small children some hypertrophy of the tonsils appears to be a physiological necessity rather than a pathological reaction. The tonsils in chronic tonsillitis may be large but often, especially in adults, are small and flat and concealed by the pillars of the fauces. There is a chronic infection of the crypts, especially of the crypta magna or supratonsillar fossa, from which pus may be expressed. A chronic abscess may form in the substance of the tonsil, usually in a deep situation near the capsule.

The cheesy tonsil

Collections of epithelial scales forming cheesy masses in the crypts are often troublesome but do not necessarily indicate chronic infection. There is often a history of recurring attacks of acute tonsillitis or of quinsy, and the lymphatic glands in the neck just below and behind the angle of the jaw are generally enlarged. A deep crimson band of congestion may be seen along the anterior faucial pillar. Such tonsils may be important as sites of focal sepsis, causing arthritis, muscular rheumatism, or nephritis.

Signs and symptoms

Indigestion and retching are frequent symptoms. The breath may be foul and the patient may notice a bad taste in the mouth. There is often reflex cough with general symptoms of fatigue and anaemia from toxic absorption.

Treatment

As treatment, paints containing iodine or resorcinol may be tried in adults, and blocked crypts may be slit up with a small knife or the electric cautery. Unless there is some general contra-indication, such as pulmonary tuberculosis, it is advisable to remove the tonsils, especially if there is a history of recurrent acute tonsillitis or quinsy, or any pronounced cervical adenitis. Electrical treatment by diathermy, whether applied with the object of causing the tonsil to slough by repeated applications or merely with the object of sterilizing the tonsil by heating it, seldom gives results which are satisfactory for any length of time and moreover this treatment often causes great pain. In small children

Selection of cases for operation

Electro-therapy

simple hypertrophy or a single attack of tonsillitis is not sufficient reason for removal of the tonsils, as the need at that age for lymphoid tissue in order to develop immunity and defensive reaction leads to recurrence and hypertrophy elsewhere, especially of the adenoid tissue in the nasopharynx.

4.—CALCULUS

1487.] A calculus occasionally forms in the tonsil, generally in the supratonsillar fossa, composed mainly of calcium phosphate and carbonate in which filaments of leptothrix are embedded. They are usually quite small but in rare cases attain a large size and may be responsible for stabbing pain, which radiates to the ear, and for recurrent attacks of inflammation and suppuration in the tonsil. A large calculus, partially embedded, may set up an ulcer which simulates malignant disease or a gumma, but examination of the base of the ulcer with a probe will enable a correct diagnosis to be made. A calculus may be scooped out of the tonsil with a spoon, but it is generally simpler and more radical to remove the tonsil.

Composition

Removal

5.—REMOVAL OF TONSILS

(1)—Indications and Contra-Indications

1488.] Kaiser made prolonged observations on the effect of tonsillectomy on 4,400 school children in Rochester, New York. The operation was performed upon one half of these children, and in the control group of 2,200 the operation was recommended but not performed. The two groups were kept under observation for ten years. The benefits obtained during the first three years after the operation became less conspicuous in later years and the clinical condition of the two groups tended to become more alike. The immediate freedom from sore throats in the children who had lost their tonsils was not entirely maintained and seven years later, i.e. ten years after the operation, 10 per cent of the children who had lost their tonsils were still subject to sore throats, as against 36 per cent in this group before removal of the tonsils. The incidence of rheumatic fever proved to be 33 per cent less in children whose tonsils had been removed, but the operation did not exert any influence in the prevention of recurrent attacks of rheumatism when performed after the initial attack. It was found also that the operation does not protect against rheumatic carditis or have any influence on the incidence of chorea. It gives some slight protection against the incidence of scarlet fever, but reduces it by less than 50 per cent. The influence of tonsillectomy on the incidence of diphtheria is more pronounced. Consequently in recommending the operation on relative indications certain benefits to the child may be legitimately claimed, but these can be easily exaggerated.

*Effect on
sore throats*

*Rheumatic
fever*

*Scarlet fever
Diphtheria*

Absolute indications for tonsillectomy in children are frequently

*Indications
or
tonsillectomy*

recurring sore throats and enlargement of the cervical lymphatic glands. Nasal obstruction and otorrhoea in the absence of caries of the middle ear are indications for the removal of adenoids but not necessarily of tonsils, and in small children preservation of the tonsils is the best guarantee against recurrence of the adenoids.

*Tuberculous
infection of
tonsils*

About 5 per cent of the tonsils removed from children show histological evidence of tuberculosis, and it is probable that this is not of much clinical significance; but when the tonsils are removed on account of gross enlargement of the cervical lymphatic glands the percentage showing tuberculous lesions is much higher. The infection is usually of the bovine type.

(2)—Operative Technique*Choice of
method*

In children up to the age of fifteen it is usually possible to remove tonsils entire by the guillotine; this can also be carried out in many adults, but as a rule in order to ensure complete removal dissection is preferable. The choice of operation in individual cases is determined by the practice of the operator, but when there is a history of quinsy the line of cleavage around the capsule is difficult to define and the guillotine operation may be impossible. Whichever method is employed the whole tonsil should be removed, especially the lower pole from which the tonsil may reproduce itself. In exceptional cases, even when the tonsillectomy has been complete, the tonsil may be reproduced from the lingual tonsil and provide a target for the critical.

*Regeneration
after
removal**Anaesthetic*

In children a general anaesthetic is required, but ethyl chloride is sufficient for the guillotine operation. In adults a longer general anaesthesia is necessary. Intratracheal gas and oxygen is often used but is not suitable as it increases the bleeding. In adults local anaesthesia is often employed. A light application of 5 per cent solution of cocaine hydrochloride is made to the fauces, but this is not essential. Procaine hydrochloride (novocain) with adrenaline is then injected into the fauces around each tonsil in five spots, one above and two each in front of and behind the tonsil. The risk of post-operative haemorrhage and of blood escaping through the larynx down the trachea is greater than with general anaesthesia.

*Technique of
guillotine
operation*

In using the guillotine (see Fig. 3) the patient lies supine with the shoulders a little raised and the head extended. The mouth is opened with a Doyen gag placed between the front teeth, but not wide enough to stretch the anterior faucial pillars. The ring of the guillotine held in the right hand is passed under the lower pole of the right tonsil with the handle pointing to the left of the patient. The handle is then depressed so that the tonsil is levered on to the alveolar eminence at the posterior end of the mylohyoid ridge which forces it through the ring. To complete this movement the forefinger of the left hand is applied to the anterior faucial pillar and the whole tonsil can be felt to slip through the ring. The blade is then pushed home by the thumb of the right hand. Care must be taken that the blade passes between the anterior pillar and the tonsil so that the edge of the pillar is not nipped. The tonsil is then removed by pronating the hand. The left tonsil is removed by changing the guillotine to the left hand, or by standing behind the head of the patient. By this method the tonsil with its supratonsillar fossa is removed

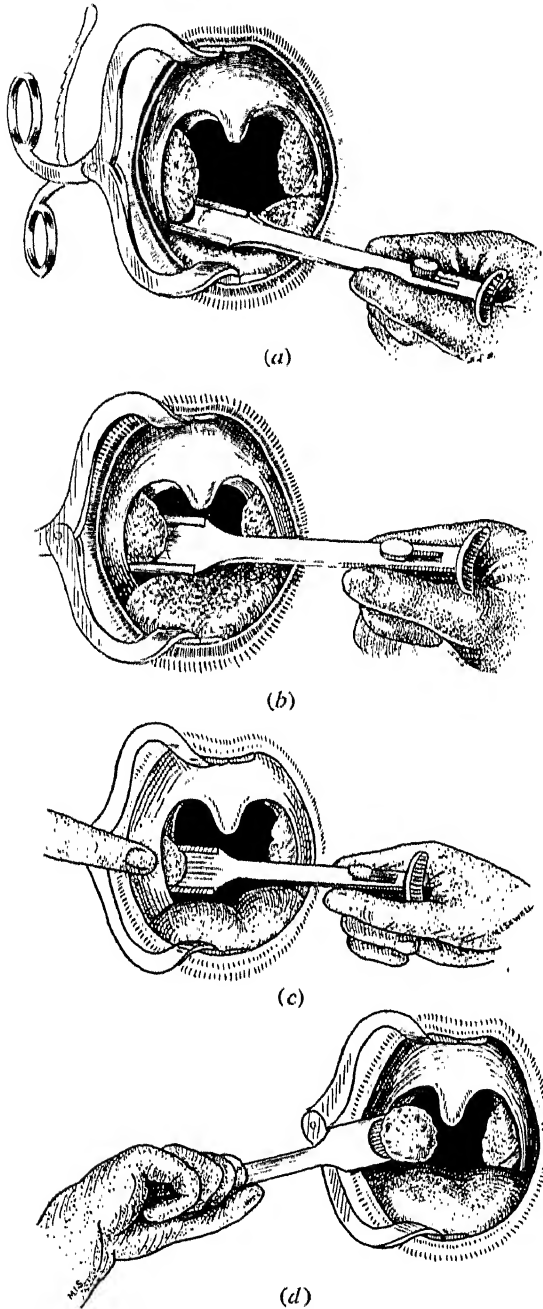


FIG. 3.—Tonsillectomy by the guillotine method. (a) The ring of the guillotine is placed under the lower pole of the tonsil to encircle it. (b) The tonsil is hooked forwards with the ring of the guillotine. (c) With the forefinger of the free hand the tonsil is pressed through the ring by applying pressure over the anterior faucial pillar. (d) When the tonsil is felt to slip completely through the ring the blade is pushed home and the tonsil is removed by pronating the hand. (This and Fig. 4 from the *British Medical Journal*, 1938)

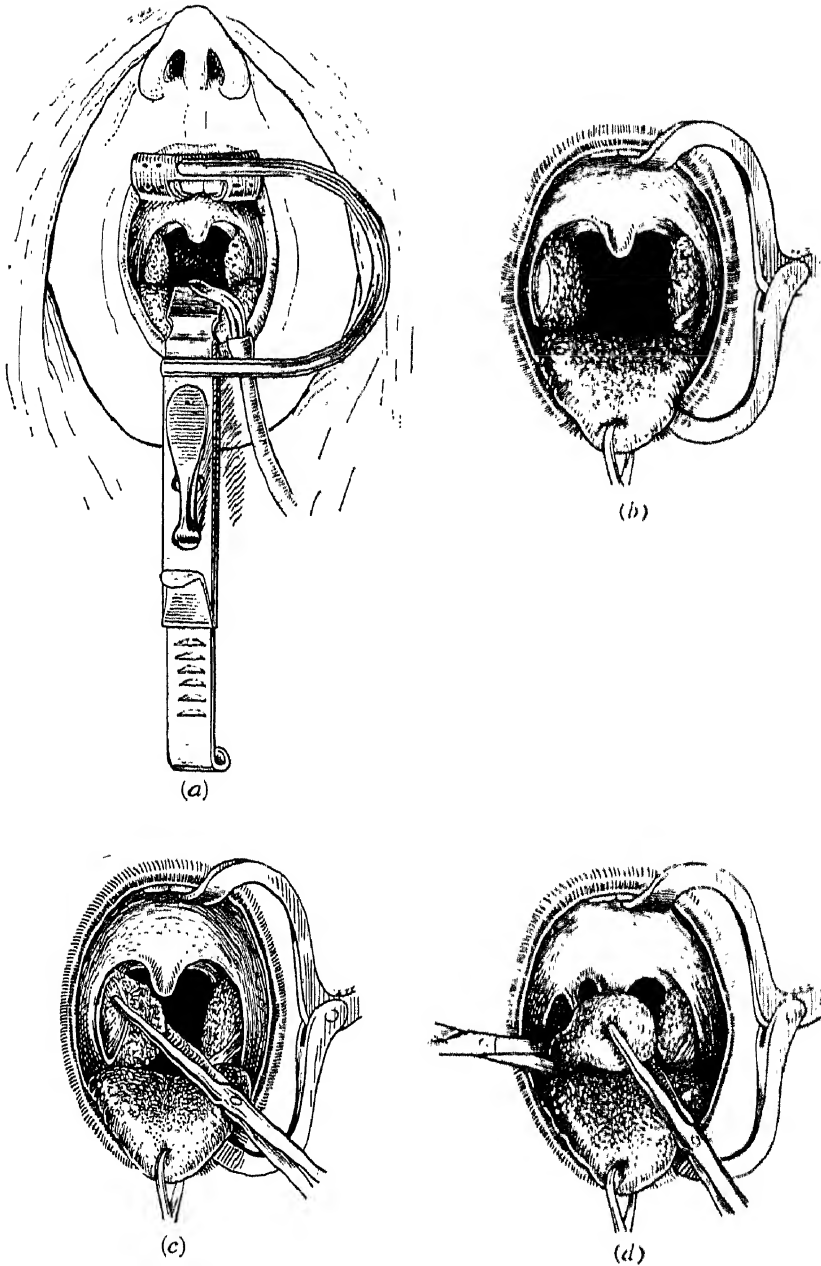


FIG. 4.—Tonsillectomy by dissection. (a) The Davis gag in position. The operator may stand at the head of the table or at the side. If at the head of the table, this figure should be seen reversed. (b) The incision in the mucous membrane covering the tonsil beneath the anterior pillar is shown. (c) The tonsil is grasped with forceps and drawn out of its bed. It is freed by blunt dissection with long-handled forceps. (d) The tonsil is dissected out of its bed and divided with long-handled scissors below the lower pole close to the base of the tongue

complete in the capsule which is often everted in the process. Two sizes of guillotine should be available.

In removal by dissection (see Fig. 4) the patient may either lie supine with the head dropping far back or tilted over on the right side. If local anaesthesia is used the patient sits in a chair and depresses the tongue himself. *Removal by dissection*

Under general anaesthesia the mouth is opened with a Doyen or Sydenham gag, but many operators prefer to use the Davis gag which gives a good view of the tonsils by forcing down the base of the tongue, with the patient lying on the back, but this has the disadvantage that the mouth cannot be fully opened and pressure is often made on the front of the neck. The tongue is drawn forwards with a tongue clip or silk thread passed through the tip. The reflection of mucous membrane between the anterior pillar and the tonsil is incised or torn through with scissors or long-bladed dissecting forceps. Suitable forceps must be used to hold the tonsil and draw it out of its bed. The dissection is best done by teasing out the tonsil with the long-bladed dissecting forceps so that the vessels are torn across and retract. There is then very little bleeding and ligatures are seldom required. The tonsil is thus shelled out of its bed but it often remains attached at the lower pole to the lingual tonsil at the base of the tongue from which it must be divided with scissors.

Careful sponging or the use of an electric suction pump is necessary to keep the field of operation clear from blood. The only vessel likely to bleed persistently is the tonsillar branch of the facial artery which enters the tonsil about the middle of the tonsil bed on the posterior pillar. If it does not retract it should be picked up with long forceps and ligatured with silk, but bleeding may continue after the guillotine operation from a button-holed vein which cannot retract. If there is a persistent oozing of blood or post-operative haemorrhage, ligatures of fine silk on a Reverdin's needle should be passed across the tonsil bed or through both pillars and tied. The stitches should be removed on the following day and not allowed to cut out, if they have been passed through the pillars. If reactionary haemorrhage occurs several hours after the operation there should be no hesitation in taking the patient back to the operating theatre and controlling the haemorrhage under an anaesthetic. *Treatment of bleeding*

If the mucous membrane covering the edge of the anterior pillar is kept intact there is usually not much post-operative pain, but this varies and may be controlled by euphagin or aspirin applied locally in a gargle. Adults may receive an injection of morphine on the night following the operation. Soft food should be given for a few days, and anything like biscuits or crusts avoided. Children welcome ice-cream. A purge should be given on the day following the operation, as some blood is always swallowed and causes digestive disturbance; cascara sagrada is suitable, but saline purgatives should be avoided as they are extremely painful to swallow. *Post-operative treatment*

For keratosis and tumours of the tonsils see PHARYNX DISEASES, Vol. IX, pp. 576 and 580.

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TORTICOLLIS

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Reference may also be made to the following title:

HEMIATROPHY AND HEMIHYPERTROPHY

1.—DEFINITION

(*Synonym.*—Wry neck)

1489.] This deformity is characterized by lateral deviation and rotation of the head. It arises from various causes, but in nearly all cases the basic feature is contraction of one sternocleidomastoid muscle, with consequent approximation of the mastoid process to the sternoclavicular joint. As a result, the head is flexed to the affected side and rotated towards the opposite side. In long-standing cases secondary changes develop in adaptation to the altered position.

2.—TYPES

(1)—Congenital

(a) *Aetiology and Clinical Picture*

The congenital is the common type. The deformity, though labelled congenital, is not present at birth, but develops in childhood and gradually increases during adolescence.

It is attributed by some to congenital aplasia of the sternocleidomastoid muscle. According to this view the muscle is imperfectly formed and fails to grow at a rate commensurate with the general development of the body. Its relative shortness becomes more marked in later childhood, and thus the deformity becomes apparent. A second view, supported by many authorities, is that the deformity follows injury to the sternocleidomastoid sustained at birth. It has been claimed that wry neck is commonest after difficult labours, and especially after breech presentations, in which the neck muscles are peculiarly liable to injury (see MUSCLES DISEASES, Vol. IX, p. 14).

In a small proportion of cases there is a history that a few weeks after birth a lump was noticed in the neck, the so-called sternomastoid tumour. According to Brooks, Middleton, and others, this swelling is a result of venous infarction of the muscle, due to prolonged obstruction of the venous return from this part of the neck during parturition. The 'tumour' is a spindle-shaped enlargement of the muscle, and microscopic examination shows that it consists of granulation tissue and young fibrous tissue containing degenerated muscle cells. In the course of time the swelling subsides and is replaced by tough scar tissue which, by contraction, leads to the wry-neck deformity.

In the fully developed case the deformity is obvious. The head is bent towards the affected side and at the same time rotated towards the opposite side. Thus, if the right sternocleidomastoid is affected the head is approximated towards the right shoulder, the face is turned towards the left, and the chin is up-tilted. The movements of the head and neck are greatly restricted, especially those that involve stretching the affected muscle. The sternocleidomastoid can be seen and felt as a tense contracted band of fibrous tissue.

In long-standing cases secondary changes follow: all the soft tissues on the affected side of the neck undergo adaptive shortening, including the deep fascia, the muscles of the neck, the carotid sheath, and the large vessels. The mastoid process at the insertion of the muscle is hypertrophied. The skull acquires an oblique deformity. A compensatory scoliosis may develop. Finally, and most significant, the face undergoes hemiatrophy, all the features on the affected side being smaller and closer together than on the opposite side. The importance of this last feature is that in long-standing cases the hemiatrophy persists, and even though the wry-neck deformity is corrected, there remains an obvious asymmetry. (See also Vol. VI, p. 420.)

(b) Treatment

The treatment is by operation. This should not be delayed unduly owing to the risk of secondary deformities, such as facial atrophy, which will not respond to treatment. In mild cases the operation of subcutaneous tenotomy suffices.

The sternocleidomastoid is put on the stretch over a sand-bag placed between the shoulder blades. A tenotomy knife is then inserted through a

skin puncture low in the neck, immediately above the clavicle, and the tense fibrous bands which represent the sternal and clavicular heads of the muscle are divided. The other tight structures are then stretched by manipulating the head into an over-corrected position.

Open operation

In more severe cases an open operation is advisable. The incision most suitable as a general rule is oblique and placed in the natural fold of the skin a short way above the clavicle. It is deepened to expose the lower end of the sternocleidomastoid muscle and a wide area in the lower part of the neck. The sternal and clavicular heads of the muscle, the deep fascia of the neck, and all other tight structures are divided, and finally the tissues of the carotid sheath are dissected off the large vessels and removed. An additional step favoured by some authorities is to make a second incision in the upper part of the neck to divide the upper attachment of the muscle close below its insertion.

After-treatment

The after-treatment is of special importance, for there is a great tendency to recurrence of the deformity, however radical the operative dissection has been. The child will prefer to revert to his accustomed attitude, and persistent correction is necessary to ensure a good result. The best method is to fit a piece of poroplastic felt to sit snugly on the affected side of the neck, where it is fixed in position by a bandage. The felt is cut and moulded to fit the neck and is made just wide enough to exert a little upward pressure on the mastoid process and the angle of the jaw, in that way maintaining the corrected position. In addition, regular exercises should be carried out under the supervision of a masseuse.

(2)—Acute

Sequel to fibrositis or myositis

This term includes a number of affections in which the wry neck comes on rapidly and does not persist. The commonest is due to fibrositis or myositis and is generally attributed to 'catching a chill'. The neck is acutely stiff, and the affected muscles are felt to be tightly in spasm and acutely tender. After a few days the condition passes off. Treatment consists in the application of heat, gentle massage, and administration of aspirin or similar drugs.

Sequel to infection of lymph glands

Wry neck may also occur acutely as a result of an infection of the lymph glands in the neck, especially of the glands along the accessory nerve, deep under the sternocleidomastoid muscle. In most cases the glandular enlargement is due to infection from the ear, nose, or throat. The neck is stiff, and there is acute tenderness over the affected glands. The treatment is to keep the patient in bed at rest, to apply heat to the neck, generally in the form of fomentations, and to employ any measures required for the primary infective focus.

Sequel to spinal lesions

Lastly, acute wry neck may result from injury or disease affecting the cervical portion of the spine or cord. Thus it may follow unilateral dislocation of the cervical spine or tuberculosis of the spine. In either case, if due attention is paid to the history and to the physical examination there is little difficulty in the diagnosis.

(3)—Spasmodic

This is a rare affection, which is characterized by spasmodic rotatory movements of the head. The movements are jerky and recur incessantly. They are, however, completely absent during sleep. In addition to the sternocleidomastoid muscles, the trapezius is often involved, and sometimes also the complexus, splenius, and oblique muscles of the opposite side.

Spasmodic wry neck occurs mainly in adults of neurotic disposition *Causation* and generally starts after severe overwork or mental strain. It is now regarded as a functional nervous disorder.

The treatment in most cases is directed towards improving the general *Treatment* health and obviating all sources of nerve strain or worry. If these measures fail, some benefit may be obtained by resecting the accessory nerve at a point above its entrance into the sternocleidomastoid muscle. It is sometimes advised also to divide the upper cervical nerves of the opposite side in order to paralyse the synergistic muscles, but this procedure is rarely beneficial.

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TORULOSIS

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1.—DEFINITION

1490.] Torulosis is a rare disease in which a yeast-like fungus, *Torula histolytica*, invades the central nervous system and more rarely the lungs and other viscera. The onset is generally gradual with severe headache; this is followed by stiffness of the neck, vomiting, and failing vision. Later, paralysis and convulsions may supervene. Fever is often absent, emaciation is prominent, and the course is generally progressively downward. Though the prognosis is fatal in systemic and cerebro-spinal torulosis, rare localized infections of the vertebrae, tongue, and nasopharynx have been followed by recovery.

2.—AETIOLOGY

Torulosis in man was first adequately studied by Stoddard and Cutler (1916), who named the fungus *Torula histolytica* and differentiated the disease from blastomycosis and coccidioides. *Torula histolytica* is a highly refractile, double-contoured, spherical or oval, yeast-like organism. In the tissues and on culture media it reproduces only by budding. It is distinguished from other fungi by the absence of mycelia and spore formation, the frequent presence of a capsule, and a minimal

The
organism

tendency to ferment sugars. There appear to be two or three varieties. The organism is pathogenic to mice and rats and to a less degree to guinea-pigs and rabbits.

*Pathogenicity
to animals*

All races appear to be equally susceptible. The disease occurs twice as often in males as in females and is most common from the ages of 30 to 60 years; occasional cases have been reported in childhood. The portal of entrance is probably the sinuses, tonsils, or lower respiratory tract, whence the torulae travel by the lymphatics or the blood-stream to the central nervous system and elsewhere in the body.

Incidence

*Route of
invasion*

3.—MORBID ANATOMY

Torula invasion generally results in the formation of granulomas, the lesions resembling somewhat those seen in tuberculosis, syphilis, and certain mycotic diseases. Inflammatory reaction is more marked outside the central nervous system, and the lesions consist of small tubercles or nodules varying in size from 0.5 mm. to 1.0 cm. Cyst-like spaces containing gelatinous material may form in the tissues, and in one case of pulmonary and cerebral torulosis which I investigated the lungs on section presented the appearance of honeycomb filled with gelatinous exudate. In generalized infections the kidney, spleen, lymph nodes, bone marrow, liver, adrenal, thyroid, tonsils, and skin and subcutaneous tissues have been implicated.

*Macroscopic
changes*

The central nervous system is almost invariably involved and three types of lesion have been described by Freeman: (i) a diffuse or focal granulomatous meningitis resembling somewhat tuberculous meningitis with thickening and matting together of the meninges which become adherent to the cerebral cortex and the base of the brain; (ii) a perivascular form due to torulae extending along the perivascular sheaths of the vessels forming flask-shaped cysts in the upper layer of the cortex, and giving rise to the appearances of 'soapsuds, blisters or pits'; (iii) an embolic form with deeply placed granulomas and cysts involving the grey matter of the basal ganglia or the white matter of the cerebrum and cerebellum. In rare cases the spinal cord may be involved by a chronic torular meningitis and granulomatous nodules which may produce spinal compression (Smith and Crawford).

*Central
nervous
system*

The meninges show endothelial hypertrophy, round-cell infiltration, foreign-body giant cells, and fibrosis. The torulae are numerous. The gelatinous cysts are caused mechanically by the accumulation of large numbers of torulae with minimal reaction of the mesodermal elements, and the granulomas are composed of masses of endothelial cells, many of which contain the invading organism. Neuroglial reaction is minimal. The mode of production of the clear gelatinous zone around the micro-organisms is unknown. No evidence is available that it is due to any digestive action exerted by the torulae on the tissues and, as Freeman pointed out, the original term 'histolytica', introduced by

*Microscopic
changes*

Stoddard and Cutler to describe the organism, is a misnomer. Probably the gelatinous material originates as a secretion or as some by-product of the metabolic activity of the torulae.

*Blood
picture*

In the cerebrospinal form there is usually a moderate leucocytosis which varies from 7,000 to 25,000 cells per c.mm., and the differential count not uncommonly shows an increase in the polymorphonuclear neutrophil leucocytes. Decreased red-cell counts and haemoglobin values occur only in the late phases of the disease. No noteworthy clinical biochemical findings have been recorded. Torulae have been found in the cerebrospinal fluid, sputum, and pus.

*Cerebrospinal
fluid*

When the central nervous system is involved examination of the cerebrospinal fluid is much the most important aspect of the laboratory investigation. The fluid is generally under increased pressure and readings as high as 700 mm. of water have been recorded. It may be colourless, slightly hazy, turbid, or even gelatinous in appearance and on standing a pellicle generally forms. The globulin and albumin contents are increased, and the sugar is either normal or decreased. The colloidal-gold curve is as a rule of meningitic type. The cell-count is increased, varying generally from about 200 to 800 cells per c.mm. Most of the cells are lymphocytic, but sometimes polymorphonuclear neutrophils constitute as much as 30 per cent of the cells present. Occasionally endothelial cells with phagocytosed torulae are found. Not uncommonly at the first examination the torulae are mistaken for lymphocytes.

4.—CLINICAL PICTURE AND COURSE

*Incubation
period*

The clinical manifestations are somewhat variable, but for clinical purposes the disease may be considered under the headings (i) localized and (ii) cerebrospinal torulosis. The incubation period has not been accurately ascertained for man, but animals develop clinical manifestations some two to four weeks after inoculation. It is probable that a somewhat similar period of incubation holds good in human infections.

Localized torulosis

Only a few instances of localized torulosis are reported. McGeehee and Michelson reported a case of pelvic abscess pointing in the inguinal region, the pus from which contained torula organisms. Pulmonary complications supervened but the patient recovered. Jones recorded torular infection of the nasopharynx responding to surgical treatment, and Jeanselme and his colleagues published a case of mycetoma in a coloured woman due to the same cause.

Cerebrospinal torulosis

The central nervous system is practically always involved in generalized torulosis so the two types need not be considered separately. In a series of 60 cases of cerebrospinal torulosis analysed by Levin (1937)

the central nervous system alone was involved in 30; in the remaining 30, in addition to the central nervous system, the lungs were involved 17 times and the skin 5 times. Other organs implicated included the tonsils, kidneys, spleen, lymphatic glands, and adrenals. The clinical features vary with the virulence of the causal organisms and the part of the nervous system which is predominantly involved. Many cases manifest evidence of increased intracranial pressure, basal meningitis, and nerve palsies.

The onset is generally insidious with frontal, fronto-temporal, or retro-ocular headaches which are intermittent at first and later become continuous. Sometimes the disease commences suddenly, when severe headache, faintness, vomiting, and vertigo are likely to be present.

Mode of onset

Often the headache is the most pronounced symptom; it may be intolerable, making the patient scream with pain, and Freeman suggested that this happened when there was wide-spread invasion of the cerebral cortex. Other symptoms, such as projectile vomiting, dizziness, vertigo, failing vision, arthritic pains, and pain and stiffness of the muscles of the neck and back, soon follow, and sleeplessness or somnolence proves very troublesome in some cases. Diplopia, amblyopia, photophobia, and even amaurosis are not uncommon.

Symptoms

Fever is generally absent, anaemia is rare, and the blood-pressure remains about normal. The pulse is apt to be somewhat increased in rate, especially if there is fever. The most common finding is stiffness of the neck associated with a positive Kernig's sign indicative of meningitis. Brudzinski's sign may be positive, the deep reflexes are often lost, and hyperaesthesia is not uncommon. According to Freeman neuro-retinitis, papilloedema, and choked disk occur in about two out of every three cases. Strabismus, fixed pupils, ptosis, and nystagmus are sometimes present. Deafness is rather rare, but other nerve palsies, hemiparesis, and hemiplegia may appear in the late stages of the disease. When the spinal cord is involved spinal compression with paralysis of the limbs may ensue. Pulmonary involvement or adenitis naturally suggests tuberculosis and only the demonstration of *Torula histolytica* by laboratory means enables a diagnosis to be made.

Signs

Torulosis generally runs a subacute or chronic course, the average duration being about four months. Acute cases are recorded which have proved fatal within three weeks, whereas two chronic cases have lasted two and a half and five and a half years. Though remissions may occur the course is progressively downward and the prognosis in the cerebrospinal type of the disease is invariably fatal. Patients with the localized type of infection may recover.

Course and prognosis

5.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In both localized and generalized torulosis the diagnosis is never made on clinical grounds and it is only the demonstration of yeast-like

Isolation of organism

organisms in the pus of local lesions, in the sputum when there is pulmonary involvement, and in the cerebrospinal fluid in cerebrospinal torulosis that establishes the diagnosis. Smears of the centrifugalized deposit should be stained with Wright's stain to differentiate the torulae from lymphocytes for which they are often mistaken. In doubtful cases the suspected material should be inoculated onto Sabouraud's maltose-agar or injected intraperitoneally into white mice which develop symptoms within one month; cultures should be incubated at both room temperature and body temperature for at least ten days before deciding there is no growth.

*Differential
diagnosis*

Tuberculous meningitis, cerebrospinal syphilis, epidemic encephalitis, tumour, abscess, and cysts of the brain, and cerebral involvement due to blastomycosis, coccidioides, and sporotrichosis may need to be differentiated from cerebrospinal torulosis. In the fungous infections other than torulosis there is generally a primary focus elsewhere. Syphilis is diagnosed from the history, by the presence of other syphilitic lesions, and by the Wassermann reaction and the other findings in the cerebrospinal fluid. Tuberculous meningitis may be closely simulated, especially if there is associated pulmonary involvement, but the frequent absence of fever and the more prolonged course of torulosis may arouse suspicion. In other cases the insidious onset, associated with signs of increased intracranial pressure, such as headache, vomiting, choked disk, and localized neurological features, has led to subtemporal or suboccipital decompression for suspected intracranial tumour.

6.—TREATMENT

*Cerebrospinal
form*

There is no specific therapy for cerebrospinal torulosis. Iodides, even in heroic dosage of 5 drachms daily, entirely failed in the hands of Shapiro and Neal. By decreasing intracranial pressure, daily lumbar puncture brings some measure of relief and undoubtedly prolongs life.

*Localized
form*

In localized torulosis radical surgical treatment is indicated and may be successful. All the accessible lesions should be resected and for this purpose Jacobson advocated the cautery knife.

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TOXIC GOITRE

See GOITRE AND OTHER DISEASES OF THE THYROID GLAND,
Vol. V, p. 606

TOXICOLOGY

I. HOMICIDAL, SUICIDAL, AND ACCIDENTAL POISONING

By G. ROCHE LYNCH, O.B.E., M.B., B.S., D.P.H.,
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II. INDUSTRIAL POISONING

By DONALD HUNTER, M.D., F.R.C.P.

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Reference may also be made to the following titles:

ABORTION

ACKEE POISONING

ALCOHOLISM

ALLERGY

BITES AND STINGS

BOTULISM

DERMATITIS DUE TO INJURY AND
POISONING

DRUG ADDICTION

DRUG ERUPTIONS

FOOD POISONING

GASSING AND POISON GASES IN WAR

LATHYRISM

LEAD POISONING

LIVER DISEASES: HEPATITIS, ACUTE
AND SUBACUTE

NEURITIS

POISONS LEGISLATION: MEDICAL ASPECTS

SKIN DISEASES: OCCUPATIONAL DISEASES

I.—HOMICIDAL, SUICIDAL, AND ACCIDENTAL POISONING

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1.-INTRODUCTION

1491.] The following table shows the total number of deaths from the commoner poisons in the years 1933-6 inclusive in England:

Poisonous gases (all forms)	-	-	-	8,127
Coal-gas (included in the foregoing)	-	-	-	7,955
Lysol (solution of cresol with soap)	-	-	-	1,071
Hydrochloric acid	-	-	-	319
Hydrocyanic acid and cyanides	-	-	-	315
Phenol and coal-tar distillates	-	-	-	275
Barbituric acid group of drugs	-	-	-	271
Ammonia	-	-	-	165
Oxalic acid and its salts	-	-	-	125
Aspirin	-	-	-	121
Strychnine and preparations containing it	-	-	-	55
Opium, morphine, and preparations containing morphine	-	-	-	54
Nicotine	-	-	-	51
Sulphuric acid	-	-	-	39
Arsenic	-	-	-	36
Phosphorus	-	-	-	23
Sodium and potassium hydroxides	-	-	-	13
Iodine	-	-	-	10
Chloroform	-	-	-	10
Nitric acid	-	-	-	9
Belladonna, atropine, etc.	-	-	-	7
Paraldehyde	-	-	-	7
Cinchophen	-	-	-	7

In most cases of poisoning a chemical analysis is required either for diagnosis during life or to establish the cause of death. Specimens of vomit, urine, faeces, and cerebrospinal fluid collected in the early stages of the illness contain the greatest amount of the poison and are consequently most suitable for dispatch to the analyst. Further, it cannot be too strongly emphasized that the whole of the specimen, not a small sample, must be sent. Although in most cases an ounce of urine is sufficient for a bacteriological examination, such a quantity sent for analysis for poison would be useless, because the analyst, having detected the poison, proceeds to determine the amount present, to assist in forming an opinion about the quantity absorbed, which can only be ascertained if the whole of the sample is available. The same remarks apply with equal force to the cadaver. The whole of the organs, not portions, should be placed in clean all-glass stoppered wide-mouthed jars (see Vol. X, p. 46), and the stomach and intestines should not be opened.

*Specimens
for analysis*

*Suspected
homicidal
poisoning
Arsenic*

*Carbon
monoxide*

At the necropsy the following whole organs should be sent for analysis: stomach with contents, liver, kidneys, spleen, and intestines; and all the urine in the bladder should also be sent. In certain cases of homicidal poisoning, notably arsenic, the following should also be sent: brain, heart, lungs, nails, and samples of the hair, skin, muscle, and bone. When the question of homicide is not likely to arise, it is generally sufficient to reserve the stomach with contents, the liver, kidneys, and the urine in the bladder. In cases of suspected carbon monoxide poisoning a tube of about one ounce of blood should be reserved, and the tube should be filled completely with the blood, so that there is no air-space at the top of the tube, which should be firmly corked, not plugged with cotton-wool.

All receptacles should be labelled with the nature of the contents, the name of the deceased, the date of the necropsy, and the signature of the person making the examination. The bottles should then be sealed and handed over to the messenger taking them to the analyst, a receipt for them obtained, and the bottles sent with the minimum of delay.

Bottles of medicine, pills, or other liquids or solids which require examination should be similarly treated.

*Poisonous
gases and
vapours*

In the case of death from gaseous poisons, e.g. hydrocyanic acid used for fumigation of houses or ships, or from the inhalation of vapours, such as carbon tetrachloride, as much blood as possible should be collected at the necropsy and placed in a bottle with a tightly fitting stopper, and both lungs should be placed in a similar jar.

*Significance
of analyst's
report*

In the sections of this article dealing with individual poisons the smallest lethal dose is indicated whenever possible and in some cases the average fatal dose. Thus it is stated that 2 grains of arsenic have caused death, but that probably 4 to 5 grains are average fatal doses. If the analyst reports that 2 grains or more have been found in the organs examined by him, the cause of death is certain. On the other hand, the finding of $\frac{1}{2}$ grain by the analyst may have equal significance if the report is read in conjunction with the known details of the illness. If the patient has died after several days' illness, the finding of $\frac{1}{2}$ grain of arsenic has just as much significance as the finding of several grains after an illness of a few hours, because poison is being excreted during each hour of the patient's life. I have so often been asked: 'How can you say that the deceased has died of the particular poison, when only $\frac{1}{2}$ grain has been found in the body, and the lowest fatal dose recorded is 4 to 5 grains?' Detection of traces of an organic poison in the organs is often sufficient evidence that a large quantity has been taken, especially when the drug in question is rapidly broken down in the body.

The examination of certain tissues, e.g. epidermal structures in the case of arsenic, is important in cases in which many doses have been given over a long period. A careful examination of the hair may enable the analyst to express an opinion about the length of time over which doses of this drug have been given. Medicinal dosage must be excluded, because the quantities found in the hair, when arsenic has been pre-

scribed for a long time, may equal those found in cases of homicidal poisoning in which several toxic doses have been given.

Although homicidal poisoning is relatively uncommon in England, *Diagnosis* probably only a proportion of such cases result in the poisoner being brought to justice. This fact calls for the greatest vigilance on the part of the practitioner, upon whom alone rests the responsibility of the diagnosis. Many cases of homicidal poisoning have not been established until after an exhumation; in such cases the practitioner was satisfied that death was due to natural causes and he gave a certificate to that effect.

The following points should be borne in mind when the diagnosis is under consideration.

(i) In many illnesses there are premonitory symptoms, but in poisoning *Prodrome* these do not occur. (ii) Most poisons taken in large doses produce *Onset of symptoms* symptoms immediately or within a short time of being taken. When several, even comparatively small, doses are given, each dose exacerbates the symptoms. (iii) Sudden acute symptoms in a person of normal health or in stationary bad health are suggestive, but often there is a natural explanation. (iv) A sudden change in the symptoms of a person suffering from some disease must be carefully considered, unless the change is characteristic of the disease. (v) Poisoning usually occurs in relation to *Relation to food* the taking of food, drink, or medicine not consumed by other persons, and a change of taste may be significant. (vi) Food poisoning usually affects all the partakers, but in homicidal poisoning there is usually one victim only. (vii) The course of the illness in poisoning is often one of *Course of illness* rapidly increasing severity followed either by death or by a recovery which is often much more rapid than in disease.

After burial, even for a very prolonged interval, most mineral poisons *Detection of poison after burial* can probably be recovered, in fact as long as there is any of the corpse left. The volatile poisons disappear in a few weeks. The organic poisons vary very much, but, unless a very long period has elapsed, an analysis is probably worth while. We have found morphine twenty months after burial.

After cremation nothing will be found except one or two uncommon *After cremation* mineral poisons.

The problems confronting the practitioner in cases of accidental and suicidal poisoning are generally simple and straightforward; namely, the application of the appropriate treatment. If the patient recovers, there is nothing further to be done, save that in cases of accidental poisoning advice about the prevention of future accidents may be given. In certain cases of industrial poisoning there may be the question of Home Office notification, and also that of compensation. In *Industrial poisoning* homicidal cases, however, there are many difficulties, and the practitioner will have a very anxious time not only in the protection of his patient but in the detection of the poisoner in order to prevent future attempts. *Homicidal poisoning*

If either personal observation or information supplied by the patient

- Investigation and treatment of suspected poisoning* or by a third person leads the practitioner to suspect foul play, each detail must be critically examined and a natural explanation sought, upon which, in most instances, the suspicions will be proved groundless. In the rare cases in which they are justified the practitioner should not communicate his suspicions to any member of the patient's household or friends, unless he is satisfied that they can be trusted, but, without betraying his motives, he must use his ingenuity to circumvent the suspected poisoner. If the suspicions were originally suggested by the patient, delusions should be excluded; if by a third person, the practitioner should beware of interested motives of that person and of an attempt made by a poisoner to implicate an innocent person.
- Nursing* A special nurse may be brought in to take over the duties of anybody suspected of being guilty and to prepare all food for the patient; but she should be acquainted with the reason only if the practitioner can rely on her co-operation. The suspected person and perhaps all other persons
- Visitors* should be forbidden to visit the patient or only allowed to do so in the presence of the nurse. If serious symptoms develop, the practitioner
- Removal of patient* should urge the removal of the patient to a hospital or a nursing home out of reach of the suspected poisoner.
- Specimens for analysis* Specimens of excreta should be reserved for analysis, especially those passed within twenty-four hours of the time of the suspected administration of poison. If the patient has alleged that he is being poisoned, he
- Cost of analysis* will presumably be willing to bear the cost of analysis; but a difficulty arises when the allegations or suspicions must be kept secret. It is obviously unfair for the practitioner to bear the cost, and a request to the police to do so may precipitate matters unduly, as explained below. The alternative is an application by the practitioner to the Under-Secretary of State at the Home Office, who may, if he thinks fit, order an analysis at the expense of public funds and can delay police action until the analyst's report has been received.
- Medicine* If it is thought that the medicine is being tampered with, the prescription may be modified, so that the addition of poison will be betrayed by a change of taste or of colour.
- Notes* Careful notes of every incident should be made at the time and kept for reference.
- Consultation* It is advisable to call in another practitioner as consultant and to communicate the suspicions to him; in this way an independent witness is secured. When the two practitioners are certain of foul play, but not before, they should communicate with the police. A premature investigation by the police, with its lengthy interrogations and perhaps detention of persons, may lead, if the suspicions are later proved groundless, to an action for damages against the practitioner and to the ruin of his practice.
- Informing the police*
- Death certificate* The practitioner must take special care in such a case when the patient is a stranger, because possibly he has been called in by the poisoner either because he does not know the patient or because, if he refuses to grant a certificate, the poisoner may have recourse to the deceased's

usual medical attendant, whom he may persuade to grant a certificate based on his knowledge of the deceased's general ill-health.

In all cases of death due to poison the practitioner must refuse a death certificate and should inform the coroner of all the circumstances as soon as possible. If poison is merely suspected, it is advisable, especially if there has been any allegation or mention of it, to inform the coroner. In some cases it may be advisable to issue a death certificate and to inform the coroner that poisoning is suspected. Before leaving the deceased's house the practitioner should take possession of all medicine bottles and glasses and any food or material suspected of containing poison, lest such possible evidence be destroyed.

The following Counsel's opinion, obtained by the Royal College of Physicians of London, sets out the legal obligations of the practitioner in cases of criminal abortion by drugs or by other means. This statement is authorized by the Royal College of Physicians and is based on Counsel's opinion obtained by them:

*Criminal
abortion*

‘ROYAL COLLEGE OF PHYSICIANS OF LONDON

‘Resolutions concerning the Duties of Medical Practitioners in Relation to Cases of Criminal Abortion:

‘The College is of opinion—

‘(i) That a moral obligation rests upon every medical practitioner to respect the confidence of his patient; and that without her consent he is not justified in disclosing information obtained in the course of his professional attendance on her.

‘(ii) That every medical practitioner who is convinced that criminal abortion has been practised on his patient, should urge her, especially when she is likely to die, to make a statement which may be taken as evidence against the person who has performed the operation, provided always that her chances of recovery are not thereby prejudiced.

‘(iii) That, in the event of her refusal to make such a statement, he is under no legal obligation (so the College is advised) to take further action, but he should continue to attend the patient to the best of his ability.

‘(iv) That, before taking any action which may lead to legal proceedings, a medical practitioner will be wise to obtain the best medical and legal advice available, both to ensure that the patient's statement may have value as legal evidence, and to safeguard his own interest, since in the present state of the law there is no certainty that he will be protected against subsequent litigation.

‘(v) That if the patient should die, he should refuse to give a certificate of the cause of death, and should communicate with the coroner.’

Although this opinion was given in cases in some which illegal operation or similar act had been performed, it is equally valid in cases in which the noxious drug was placed in the woman's hand.

In the following pages a description is given of the more important poisons.

2.—GASES

(1)—Carbon Monoxide

1492.] More deaths are due to this gas than to any other poison. Most of the deaths are suicidal, but many are accidental and only a few homicidal. Although the number of deaths is accurately known, it is impossible to estimate even approximately the number of the non-fatal cases, which appear to fall into two groups: (i) those with acute and urgent symptoms which are recovered from, and (ii) those due to regular small doses without any of the symptoms associated with acute poisoning. In the second group, in which perhaps 5 to 8 per cent of the haemoglobin becomes converted into carboxyhaemoglobin, the patients may suffer from vague disorders. Although the association of cause and effect is in most instances incapable of proof, there is evidence that some cases of the neurasthenic syndrome are due to such poisoning.

Non-fatal cases

Physical properties

Carbon monoxide is a colourless and odourless gas with a vapour density of 14, that of hydrogen being 1, the atmosphere 14.4, and carbon dioxide 22. Carbon monoxide, being slightly lighter than air, tends to rise to the top of a room, whereas carbon dioxide tends to sink; but for this fact more deaths would undoubtedly occur. Carbon monoxide, when present in sufficient concentration in air, explodes when a flame or spark comes into contact with the mixture. The gas burns with a bluish flame, as seen at the top of a clear fire. Its poisonous effect is greatly enhanced if it is inhaled with considerable concentrations of carbon dioxide. For this reason persons found dead in buildings after a fire have rarely been burnt to death; unconsciousness, or death, has generally supervened before the flames have reached them.

Coal-gas

Coal-gas contains about 14 per cent of carbon monoxide; consequently an escape from an unlit gas-burner or from a damaged pipe rapidly proves fatal. Generally the characteristic odour of coal-gas is present, but in some cases in which the leakage has occurred underground the passage of the gas through soil and the foundations of a house may so deodorize the gas that it is not readily detected by smell. Burnt coal-gas has but little odour. Defective apparatus leading to incomplete combustion, or insufficient ventilation to remove the products of combustion, takes its toll.

Sources of carbon monoxide

The following are the most important sources of carbon monoxide apart from coal-gas and the appliances in which it is burnt: coal, coke, and charcoal stoves, especially those of the enclosed type, in which the rate of combustion is controlled by the air intake; various chemical manufactures; exhaust gas from motor cars; every internal combustion engine produces carbon monoxide, the quantity produced depending on the efficiency of the engine; mine explosions, blasting operations, and gun-fire, the well known 'after damp' in a coal-mine explosion being a mixture of carbon monoxide and carbon dioxide; factory furnaces,

blast furnaces, and railway-engine smoke; and tunnels through which heat engines or internal combustion engines pass.

Carbon monoxide combines with haemoglobin, forming carboxyhaemoglobin, which, being more stable than oxyhaemoglobin, prevents oxygen from combination. The reaction, however, is reversible; therefore, if a gassed person is placed in the open air where there is no carbon monoxide, the oxygen inhaled can displace the carbon monoxide from its blood combination. The combination of haemoglobin and carbon monoxide in carboxyhaemoglobin is stated to be nearly 300 times as strong as the combination of haemoglobin and oxygen in oxyhaemoglobin; therefore, if a concentration of 0.33 per cent of carbon monoxide in pure oxygen is inhaled, the haemoglobin of the blood eventually becomes 50 per cent saturated; but, since approximately only one-fifth of the atmosphere consists of oxygen, the requisite concentration of carbon monoxide in the air to produce a 50 per cent saturation of the blood is 0.066 per cent.

Action on blood

The lowest concentration of carbon monoxide in the air that will produce symptoms of poisoning is 0.01 per cent, but such a concentration would not be lethal. Quantities above 0.07 per cent are potentially lethal, and, as the concentration rises, death is more and more certain in a shorter and shorter time.

Lethal concentrations

(a) *Acute Poisoning*

The post-mortem appearances are very variable. They depend on the degree and duration of poisoning, the treatment, and the time of survival after exposure. Very often signs of carbon monoxide poisoning accompany death from burns, the victim often being unconscious from carbon monoxide poisoning before being burnt. In the common type of case, in which the patient is found dead in a gas-filled room, there is usually no evidence of struggling. The face is composed, and the eyes are closed. The skin is pinkish, but after hypostasis has occurred the colour is confined to the hypostatic areas. The blood is fluid and almost uniformly cherry-red in veins, arteries, and tissues. Post-mortem clot is absent, except occasionally for a small shreddy remnant in the heart. The organs are all congested, cherry-red, and somewhat oedematous. Associated with the oedema there may be polycythaemia, due to concentration of the blood. The lungs are congested and oedematous, and the air-passages contain frothy fluid. There may be a few petechiae, especially on the pleurae.

Morbid anatomy

Some cases have shown red patches and even blisters in the skin. These lesions, which are not common, may be symmetrical, e.g. on both palms, or occur along the course of a nerve. They are probably due to slight irritation or injury in a state of increased capillary permeability. Artificial respiration always leaves marks of bruising.

Blisters

In rapidly fatal cases death is often accompanied by convulsions, and there may be bruising and evacuation of faeces. Petechial haemorrhages are more numerous and may be present on the skin, pleurae, pericardium,

In rapidly fatal cases

and brain. The heart is dilated, and the viscera are congested. The fluid blood is highly carboxylated. Sometimes the bone marrow and spleen, owing to their sluggish circulation, show very little change. At other times the spleen is enlarged and shows cherry-red congestion.

In a few cases in which the inhaled gas also contained considerable proportions of carbon dioxide or lacked the normal proportions of oxygen found in the air, lividity of the body may to some extent mask the characteristic bright cherry-red colour of the corpse.

When patient has been removed from gas

When the patient has been removed from the influence of the gas, the cherry-red coloration may be considerably reduced. Even after one hour's treatment it may not be easily discernible. When the circumstances do not clearly indicate the nature of the case, an unpublished observation by Newcomb may be of great value: small pieces of tissue taken for microscopy quickly lose their red colour in formal-saline, but if carboxyhaemoglobin is present the colour persists for forty-eight hours and longer. The supernatant fluid also remains coloured.

In death from coma several days after gassing

In patients who have died in coma several days after the gassing hypostatic pneumonia is generally present. The cells of the cerebral grey matter show degenerative changes, and there may be petechial haemorrhages. In some of these cases there is bilateral softening of the pallidal part of the lenticular nuclei. Hadfield associated this with the arterial siderosis found in the globus pallidus in about 50 per cent of people over twenty. Siderosis of the globus pallidus and its arterial supply is greater in the anterior half of the ganglion, which is where the softening occurs. There can be little doubt that the softenings are thrombotic in origin. With severe atheromatosis cerebral softening may be more extensive and irregular.

Symptoms

When atmospheric air containing carbon monoxide is inhaled, the percentage of haemoglobin combined with carbon monoxide steadily rises, but the first symptoms are not noticed until the 20 per cent level is reached: shortness of breath on exertion, headache, and lassitude. At 30 per cent there are severe headache, nausea, giddiness, tinnitus, and throbbing of the heart. There is considerable dyspnoea on the slightest exertion.

Other symptoms are convulsions and involuntary passage of urine and faeces in the late stages. An examination of the patient may show patches of reddish-pink discoloration of the skin and sometimes blisters, resembling those due to burns, commonly situated on the hands and feet. Glycosuria and albuminuria have been recorded.

Death

The urgent symptoms increase with the rising percentage of carbon monoxide, until at between 50 and 60 per cent unconsciousness occurs, and at 75 to 80 per cent death takes place. These figures apply to a fairly rapid rise in concentration. If, however, the carbon monoxide content of the air is such that the rise of blood carbon monoxide is very slow, unconsciousness may supervene at a lower concentration, and, if the patient remains unconscious for a long time, death may take place at the 50 to 60 per cent level. If, however, he is removed from the

atmosphere before death occurs, he may remain unconscious for some hours and may die or gradually recover. This is due to the damage to the brain cells by a long-continued anoxaemia.

When a patient is removed from the poisonous atmosphere, the carbon monoxide rapidly disappears from the blood, and a sample of blood taken $\frac{1}{2}$ to 1 hour later may fail to show any carbon monoxide or at most 5 to 10 per cent. If the person is found dead in a gas-filled room, a determination of the carbon monoxide in the blood will often show quantities of 70 to 80 per cent. *Recovery*

During convalescence headache may be troublesome, and peripheral neuritis, mainly of the lower extremities, with tenderness over the nerves, has been described. Finally, various mental disturbances with amnesia occur.

In cases in which the carbon monoxide has been derived from burnt gas and consequently the cause of the coma has not been suspected, the diagnosis has sometimes been completely missed owing to the rapid disappearance of carbon monoxide from the blood.

(b) *Chronic Poisoning*

Symptoms associated with chronic poisoning by carbon monoxide are common to other conditions; therefore diagnosis can only be made when proof is forthcoming of the exposure to the gas. Nevertheless many writers regard this condition as commoner than is usually suspected. If the diagnosis is attempted, it should be realized that concentrations of 5 to 8 per cent must be expected. The ordinary chemical and spectroscopic tests will therefore not yield positive results, and recourse to special methods must be made, such as the Hartridge reversion spectroscope. The sample of blood must be taken at the time of exposure and examined at once. *Diagnosis*

The symptoms are those generally of neurasthenia, with headache, nausea, want of energy, a tired feeling, lack of concentration, irritability, giddiness, especially on looking upwards, and ataxy. Sometimes a secondary anaemia with a lymphocytosis may be found. *Symptoms*

When chronic poisoning from carbon monoxide is suspected, it may be worth while to test the suspected atmosphere by one of the recognized chemical methods, but, for example, in a living room in which some heating apparatus is suspected, a mouse in a cage may be placed so that it will inhale any fumes from the apparatus. These animals are very sensitive to very small concentrations of carbon monoxide, and in the event of death the blood may readily be examined with the spectroscope for the presence of carbon monoxide (see Vol. II, Plate VI, facing p. 499). *Test of suspected atmosphere*

Removal of the source of carbon monoxide is the essential factor in treatment. *Treatment*

(2)—War Gases

See title GASSING AND POISON GASES IN WAR, Vol. V, p. 502.

3.—CORROSIVES

(1)—Acids

(a) *Hydrochloric Acid*

(Synonym. Spirits of salts)

Physical properties

1493.] This is a colourless liquid when pure, containing 32 per cent by weight of hydrogen chloride in solution. The strong acid readily gives off fumes of hydrogen chloride. Most cases of poisoning are suicidal.

Fatal dose

Since the action of this acid mainly depends on its concentration, it is not possible to fix the fatal dose, but death has been due to about half

Fatal period

a fluid ounce of the strong acid. The fatal period depends on the quantity taken. Death has occurred in a few minutes, but usually it occurs within twenty-four hours.

Morbid anatomy

The skin offers greater resistance to hydrochloric than to sulphuric and nitric acids, and cutaneous corrosion about the mouth is unusual; but it may be seen when the skin is thin, as in early childhood, when the exposure is prolonged, and when the acid is concentrated; the effects are generally less severe also on the mucous surfaces. In the upper food-passages the changes may be very slight. As a rule there is extensive inflammatory reddening with petechiae; the epithelium of the pharynx and oesophagus may in places be white and opaque. Unless this necrosed epithelium is detached, the underlying inflammation is obscured. Sometimes the changes resemble those produced by the more strongly corrosive acids. The stomach is usually contracted, with prominent corrugation of the mucosa which is a little hardened and slaty-grey or brownish. The corrosion, however, is often much more intense, with acid necrosis of hæmorrhagic tissue and the formation of black sloughs, the black colour being due to acid hæmatin. The changes are more marked along the lines of the rugæ, especially upon the dependent, i.e. posterior, wall of the fundus. In severe cases perforation is common. The small intestine in typical cases is only slightly affected. Strong acid corrosive effects due to inhalation of fumes are common and include oedema of the larynx, petechial reddening of the trachea and bronchi, and congestion and oedema of the lungs.

Symptoms

There is immediate burning pain from the mouth to the stomach and radiating over the abdomen. The skin round the mouth and the mucous membrane of the mouth and throat are destroyed, being whitish at first but soon becoming brownish and separating in shreds. The voice is husky, and there are retching and vomiting, the vomit containing shreds of mucous membrane and altered blood, which is strongly acid. There are shock and collapse, with a rapid feeble pulse, coldness in the extremities, clammy sweating, thirst, and depression.

Acid burns are often seen on the clothing.

Owing to the volatility of hydrogen chloride, or when some of the liquid reaches the air-passages, there may be inflammation of the glottis and larynx and later oedema of the lungs, with dyspnoea and the usual physical signs. Constipation is the rule. Perforation of the stomach is

common. Should the patient survive, strictures of the oesophagus or of the pylorus may occur. The gastric mucosa is largely destroyed with loss of function, and eventually surgical treatment for the relief of stricture may be necessary.

Prognosis is bad in the patients who recover from the acute symptoms. *Prognosis*

Alkalis should be administered immediately, but carbonates and bicarbonates must be avoided because they generate carbon dioxide, which may distend and burst the stomach. Since the patient has dysphagia, the alkalis should be given in solution; the best preparation is saccharated solution of calcium hydroxide (lime-water), but in an emergency soap solution may be utilized. Demulcents may also be given, e.g. milk, oil, albumen, and barley water. Morphine is necessary to relieve pain, and the state of shock will require suitable remedies. Occasionally the condition of the glottis necessitates tracheotomy. The stomach-tube must not be used on any account. *Treatment*

(b) Nitric Acid

(*Synonyms.*—Aqua fortis; red spirit of nitre)

This is usually a colourless liquid but is sometimes reddish-brown owing to the presence of oxides of nitrogen. The ordinary strong acid contains 70 per cent by weight of nitric acid, HNO_3 , but there is also manufactured a stronger preparation, fuming nitric acid, which is always reddish-brown and contains about 94 per cent by weight of nitric acid. Both strengths readily give off acid fumes. *Physical properties*

The fatal dose and period are the same as for hydrochloric acid (see p. 70). *Fatal dose and period*

Though it is interfered with by other colour changes, the most striking feature at necropsy is the bright yellow coloration of the xanthoproteic reaction. The circumoral skin is almost always stained, because the acid reacts so readily with the dead keratin. Evidence of deeper corrosion, however, is less frequent. On the mucous surfaces the effects may be as severe as with sulphuric acid. They depend on the concentration, dose, treatment, and time of exposure. Two grades or stages of corrosion can be recognized: (i) epithelial necrosis and yellow staining associated with inflammatory and petechial reddening; and (ii) deeper necrosis of haemorrhagic tissue with the massive formation of acid haematin. The changes of the first grade are diffuse. Those of the second follow where there are much friction and muscular movements which break up the caked necrotic surface and expose the deeper layers. The changes are usually most pronounced in the fundus of the stomach, where the bulk of the poison is accommodated. Perforation of the stomach here, before or after death, is not uncommon. *Morbid anatomy*

In a typical case the mucous membrane of the mouth, pharynx, and oesophagus is mottled yellow and red. In the lower end of the oesophagus and where it crosses the bronchus the wall may be thickened, dark greenish-brown or black, the friable surface being broken up and flaking. The pillars of the fauces, the upper part of the epiglottis, and

3.—CORROSIVES

(1)—Acids

(a) *Hydrochloric Acid**(Synonym.—Spirits of salts)**Physical properties*

1493.] This is a colourless liquid when pure, containing 32 per cent by weight of hydrogen chloride in solution. The strong acid readily gives off fumes of hydrogen chloride. Most cases of poisoning are suicidal.

Fatal dose

Since the action of this acid mainly depends on its concentration, it is not possible to fix the fatal dose, but death has been due to about half

Fatal period

a fluid ounce of the strong acid. The fatal period depends on the quantity taken. Death has occurred in a few minutes, but usually it occurs within twenty-four hours.

Morbid anatomy

The skin offers greater resistance to hydrochloric than to sulphuric and nitric acids, and cutaneous corrosion about the mouth is unusual; but it may be seen when the skin is thin, as in early childhood, when the exposure is prolonged, and when the acid is concentrated; the effects are generally less severe also on the mucous surfaces. In the upper food-passages the changes may be very slight. As a rule there is extensive inflammatory reddening with petechiae; the epithelium of the pharynx and oesophagus may in places be white and opaque. Unless this necrosed epithelium is detached, the underlying inflammation is obscured. Sometimes the changes resemble those produced by the more strongly corrosive acids. The stomach is usually contracted, with prominent corrugation of the mucosa which is a little hardened and slaty-grey or brownish. The corrosion, however, is often much more intense, with acid necrosis of haemorrhagic tissue and the formation of black sloughs, the black colour being due to acid haematin. The changes are more marked along the lines of the rugae, especially upon the dependent, i.e. posterior, wall of the fundus. In severe cases perforation is common. The small intestine in typical cases is only slightly affected. Strong acid corrosive effects due to inhalation of fumes are common and include oedema of the larynx, petechial reddening of the trachea and bronchi, and congestion and oedema of the lungs.

Symptoms

There is immediate burning pain from the mouth to the stomach and radiating over the abdomen. The skin round the mouth and the mucous membrane of the mouth and throat are destroyed, being whitish at first but soon becoming brownish and separating in shreds. The voice is husky, and there are retching and vomiting, the vomit containing shreds of mucous membrane and altered blood, which is strongly acid. There are shock and collapse, with a rapid feeble pulse, coldness in the extremities, clammy sweating, thirst, and depression.

Acid burns are often seen on the clothing.

Owing to the volatility of hydrogen chloride, or when some of the liquid reaches the air-passages, there may be inflammation of the glottis and larynx and later oedema of the lungs, with dyspnoea and the usual physical signs. Constipation is the rule. Perforation of the stomach is

common. Should the patient survive, strictures of the oesophagus or of the pylorus may occur. The gastric mucosa is largely destroyed with loss of function, and eventually surgical treatment for the relief of stricture may be necessary.

Prognosis is bad in the patients who recover from the acute symptoms. *Prognosis*

Alkalis should be administered immediately, but carbonates and bicarbonates must be avoided because they generate carbon dioxide, which may distend and burst the stomach. Since the patient has dysphagia, the alkalis should be given in solution; the best preparation is saccharated solution of calcium hydroxide (lime-water), but in an emergency soap solution may be utilized. Demulcents may also be given, e.g. milk, oil, albumen, and barley water. Morphine is necessary to relieve pain, and the state of shock will require suitable remedies. Occasionally the condition of the glottis necessitates tracheotomy. The stomach-tube must not be used on any account. *Treatment*

(b) *Nitric Acid*

(*Synonyms*.—Aqua fortis; red spirit of nitre)

This is usually a colourless liquid but is sometimes reddish-brown owing to the presence of oxides of nitrogen. The ordinary strong acid contains 70 per cent by weight of nitric acid, HNO_3 , but there is also manufactured a stronger preparation, fuming nitric acid, which is always reddish-brown and contains about 94 per cent by weight of nitric acid. Both strengths readily give off acid fumes. *Physical properties*

The fatal dose and period are the same as for hydrochloric acid (see p. 70). *Fatal dose and period*

Though it is interfered with by other colour changes, the most striking feature at necropsy is the bright yellow coloration of the xanthoproteic reaction. The circumoral skin is almost always stained, because the acid reacts so readily with the dead keratin. Evidence of deeper corrosion, however, is less frequent. On the mucous surfaces the effects may be as severe as with sulphuric acid. They depend on the concentration, dose, treatment, and time of exposure. Two grades or stages of corrosion can be recognized: (i) epithelial necrosis and yellow staining associated with inflammatory and petechial reddening; and (ii) deeper necrosis of haemorrhagic tissue with the massive formation of acid haematin. The changes of the first grade are diffuse. Those of the second follow where there are much friction and muscular movements which break up the caked necrotic surface and expose the deeper layers. The changes are usually most pronounced in the fundus of the stomach, where the bulk of the poison is accommodated. Perforation of the stomach here, before or after death, is not uncommon. *Morbid anatomy*

In a typical case the mucous membrane of the mouth, pharynx, and oesophagus is mottled yellow and red. In the lower end of the oesophagus and where it crosses the bronchus the wall may be thickened, dark greenish-brown or black, the friable surface being broken up and flaking. The pillars of the fauces, the upper part of the epiglottis, and

the back of the buccopharynx may be similarly affected. There may be considerable oedema of the vallecule and laryngeal vestibule. In the stomach the black sloughing mucosa of the fundus may be coated with black tarry blood. Usually the pyloric end of the stomach shows less severe corrosive inflammatory changes, which extend for a variable distance into the small intestine. Bile staining, which in this region must be distinguished from the xanthoproteic coloration, is not so bright and opaque and does not react to ammonia. The lungs are congested, and especially with the strong and 'fuming' acids there may be corrosive changes in the air-passages. The other organs show parenchymatous degeneration. The remote effects are similar to those of sulphuric acid (see p. 73).

Symptoms In general the symptoms of nitric acid poisoning are similar to those of hydrochloric acid poisoning (see p. 70), but the staining of the mouth is bright yellow, due to the xanthoproteic reaction. The vomit may contain, in addition to altered blood, bright yellow shreds of detached mucous membrane. The action of the acid on the tissues leads to the formation of gas; consequently distressing acid eructations are common. Respiratory embarrassment may require tracheotomy, and some hours after the taking of the poison there may be bronchitis and acute oedema of the lungs.

Treatment Treatment should follow the lines indicated on page 71, but, in view of possible pulmonary complications, which are much more likely to occur than in hydrochloric acid poisoning, it is desirable to support the patient on pillows.

(c) *Sulphuric Acid*

(*Synonym.*—Oil of vitriol)

Physical properties This, when pure, is a colourless oily liquid containing 95 to 98 per cent of the acid, H_2SO_4 . It is a powerful dehydrating agent, and when added to water, produces a considerable rise in temperature of the mixture. Organic substances are readily charred when brought into contact with the strong acid.

Causes of poisoning It has been used in mistake for oil, glycerin, and syrups with fatal results and has actually been put in the ear. The crime known as vitriol throwing consists of projecting some of the strong acid at the victim.

Fatal dose and period The fatal dose and period of survival are the same as for hydrochloric acid (see p. 70).

Morbid anatomy The post-mortem changes vary with the strength and dose. With accumulator acid (strength about 25 per cent) they resemble those seen with hydrochloric acid (see p. 70). When the acid is highly concentrated, however, dehydrative charring is a distinguishing feature. The charred areas are brownish to black, but blackening, as with other acids, is due mostly to acid necrosis and the formation of acid haematin. Corrosion with blackening of the lips and circumoral skin is almost constant. The tongue is greatly swollen, the mucous membrane being opaque white or brown. The teeth are chalky white and lustreless. The fauces, epiglottis,

and back of the pharynx are severely corroded. The aryepiglottic folds are swollen, laryngeal oedema being sometimes the cause of death, especially in children on account of their small size. The oesophagus is contracted, corrugated, and swollen; where it crosses the bronchus and at its lower end there is generally severe corrosion, the lesions being sometimes linearly arranged along the folds. Occasionally the changes in the passages above are surprisingly slight and are nearly always less severe than in the stomach. In this organ the changes are less towards the pyloric end and may be confined to the rugae, which are blackened and eroded. In severe cases the wall is extensively damaged, being black, friable, and often perforated. Perforation with escape of the stomach contents into the peritoneal cavity is associated with superficial blackening of the adjacent viscera; usually perforation is the result of post-mortem corrosion; when it has occurred before death, the quantity escaping into the abdominal cavity may be considerable and peritonitis may follow. Owing to post-mortem diffusion of the acid the blood in the large vessels of the trunk may be tarry or inspissated, like sticks of liquorice. The small intestine is usually affected for only a short distance, the lesions being most marked on, or confined to, the transverse folds. Sometimes, however, lesions occur even in the lower ileum.

The body shows signs of dehydration. The liver may be fatty, and there may be parenchymatous degeneration in other organs. The lungs are congested and may show acid digestion. When the poison has been directly aspirated into the lungs, destruction of the soft and skeletal structures of the thorax may be very striking. Broncho-pneumonia is unusual and present only when death has been delayed for a few days.

In patients who have recovered from the immediate symptoms but have succumbed later to the cicatricial scarring in the oesophagus and stomach there are the changes of inanition cachexia.

When this acid comes into contact with the skin, it causes great pain, burning, and permanent scarring. Should any reach the eye, blindness commonly results. Owing to its dehydrating and charring effects the symptoms are even more severe than those seen with the other mineral acids, but, unless any of the acid reaches the air-passages, respiratory embarrassment is not likely to occur. The tongue rapidly swells, the corrosion extending to the deeper layers. Salivation is profuse and, owing to the pain and corrosion of the throat, swallowing is very difficult. There are extreme thirst, retching, and vomiting of black material, which is partly altered blood and partly charred shreds of mucous membrane. Collapse and shock are severe. Perforation of the stomach is common. Unless a very small dose has been taken, recovery is not common, but when it occurs there are generally formation of strictures and loss of gastric function.

Treatment is essentially the same as for hydrochloric acid (see p. 71), but the excessive dysphagia renders difficult the administration of antidotes. Morphine is always necessary for pain.

(2)—Alkalis

(a) *Potassium and Sodium Compounds*

1494.] The caustic alkalis comprise potassium hydroxide, strong concentrations of potassium carbonate, sodium hydroxide, and strong concentrations of sodium carbonate. The hydroxides are commonly prepared in stick form and are deliquescent solids.

Fatal dose Since concentration plays a very important part in the effects of poisoning by these substances, it is difficult to fix an average fatal dose. Probably about half an ounce of the hydroxide and larger quantities of the carbonates would have to be taken to produce death.

Fatal period The period during which death may occur largely depends on the quantity taken; when large doses have been swallowed, death may follow in about twelve hours or, if the acute phase is recovered from, death may be delayed for weeks. In more than half the fatal cases death is due to inanition or to accidents attending the treatment of cicatrices produced by the poison.

Morbid anatomy The post-mortem appearances differ entirely according as death occurs early from caustic corrosion or late from cicatricial stenosis, this difference being determined in the first place by the concentration and the dose of the poison swallowed, the degree of corrosion depending on the concentration, and the anatomical distribution of the lesions on the dose.

In acute cases the following appearances are commonly met. The lips, cheeks, gums, and tongue are swollen. In the pharynx and the oesophagus (where it crosses the left bronchus and at the lower end) the corrosion is more severe. The wall is swollen by oedema, and the necrotic surface is haemorrhagic and fibrinous. As a rule patches of haemorrhagic necrosis, brownish from the formation of alkaline haematin, are present in the stomach; since they tend to occur on the dependent parts, the lesser curvature may escape and the posterior wall be affected most. The contents are usually brownish owing to altered blood. In most cases, especially as the result of treatment, they are acid. In very marked contrast to what happens in poisoning by strong mineral acids, perforation is extremely rare. It would appear that the acidity of the gastric secretion is to some extent protective. In these cases death is due to shock, and the right heart is found empty. In other cases death is the result of asphyxia from laryngeal corrosion and subsequent oedema; this is more likely to occur in children owing to the small size of the larynx. When death is delayed for several days it may be due to aspiration broncho-pneumonia.

Cicatricial stenosis

In patients who succumb after many weeks or months there are general wasting and anaemia from the starvation due to cicatricial stenosis, which is commonest in the oesophagus and especially at the following levels: the lower end, opposite the tracheal bifurcation, and the upper end. Stenosis may be single or multiple, or the whole oesophagus may be affected. The obstruction may be complete.

Cicatricial scarring may also occur in the stomach and produce pyloric stenosis or prepyloric stenosis with the formation of hour-glass

deformity. Whether or not corrosive scarring predisposes to malignant disease is uncertain, but chronic peptic ulceration may occur. The great majority of chronic cases will have undergone surgical treatment, and very often death is due to post-operative shock, broncho-pneumonia, or some accident, such as false passage by a bougie.

The degree of concentration of the poison is the important factor. *Symptoms*
When a concentrated solution is taken, a slimy soapy sensation is noticed, followed by an intense burning pain extending from mouth to stomach. The lips and tongue are swollen, the mucous surface being at first whitened but later brownish. Retching and vomiting occur immediately. The vomit, apart from food, is at first mucoid and strongly alkaline to litmus; later it is brownish and contains alkaline haematin with necrotic shreds of mucous membrane. Shock is severe, the skin being cold and clammy and the pulse rapid and feeble. There is generally diarrhoea. Patients dying from shock are clear mentally until the end. The larynx may be affected, causing a spluttering cough and dysphonia. There may be associated respiratory obstruction requiring tracheotomy, especially in children. Aspiration of material into the lungs may set up fatal broncho-pneumonia.

When the concentration has been low, the symptoms are correspondingly slight and, if treatment is prompt and energetic, there may be complete recovery. When corrosion has occurred, there will always be cicatricial contracture later. This is commonest in the oesophagus, resulting in dysphagia, which may lead to complete obstruction. The damage to the stomach will lead to loss of gastric function; the patient wastes and even with efficient treatment will be likely to die from inanition in a few weeks to a year. Perforation of the stomach in the acute stage has occurred but is uncommon.

The poison should be immediately diluted with water containing some dilute acid, e.g. vinegar or lemon juice. These acids, however, must be avoided if the carbonate has been taken, and magnesium sulphate should be substituted. Some authorities suggest the use of the stomach-tube, but this is better avoided on account of the damage that may be effected. Demulcents, e.g. white of egg, barley water, and oily emulsions, may be given. Shock must be combated, and morphine will be required to relieve the pain. Respiratory embarrassment may make tracheotomy necessary. *Treatment*

Patients who recover from the acute stage will probably require surgical treatment later for the relief of contractures in the stomach and oesophagus.

(b) *Ammonia*

The corrosive changes due to poisoning by ammonia are less intense than those due to the fixed alkalis, and the amount taken tends to be smaller because of the difficulty in swallowing ammoniacal solutions. For these reasons the percentage mortality is lower. The incidence of ammonia poisoning, however, and the total mortality are very much

greater than those of the fixed alkalis. Poisoning may occur from the escape of ammonia fumes from refrigeration plants.

Death is generally due to the effect of the ammonia gas on the air-passages. Cicatricial scarring in patients who recover is not common, because ammonia is a much weaker alkali than sodium or potassium hydroxide, and because such scarring would only be likely to occur when a considerable quantity of the concentrated poison had been taken, i.e. in cases which are nearly always fatal in the acute stage.

Fatal dose

It is almost impossible to fix the quantity which would be likely to be fatal, because the concentration of the poison is of paramount importance, and because in so many of the fatal cases neither quantity nor concentration is known; 6 fluid drachms of a 10 per cent solution have caused death in an adult.

Fatal period

When very concentrated solutions have been swallowed, or when the gas has been inhaled in concentrated form, death may follow very rapidly, i.e. in a few minutes. When the poison is less concentrated, death may be delayed and occur from respiratory embarrassment due to acute pulmonary oedema.

Morbid anatomy

The most important changes are in the respiratory tract. The vestibular part of the larynx is corroded and oedematous, and the glottis may be completely obstructed. The tracheo-bronchial mucosa is reddened, speckled with petechiae, and swollen. In severe cases fibrinous exudation on the surface may form a false membrane. Owing to these changes the lumen of the smaller bronchi may be considerably reduced. The nasal mucosa is similarly affected, and the conjunctiva may be injected or chemotic. The lungs are generally congested. They contain much frothy fluid, which is also present in the upper air-passages. The blood is dark and as a rule fluid. There may be asphyxial petechiae.

When death has been solely due to the action of the vapour, as in certain industrial accidents and sometimes after the misguided treatment of fainting by the application of strong ammonia to the nose, no other changes may be found. Generally, however, the poison has been swallowed, and corrosive lesions are present in the upper food-passages. These resemble those seen with the other caustic alkalis except for the following differences: (i) death tends to occur earlier, and the contents of the stomach are therefore more regularly alkaline; and (ii) cases with severe corrosion tend to die in the primary stages, so that late cases with cicatricial contracture are uncommon.

Symptoms

The immediate effect of the vapour on the respiratory epithelium is a sensation of suffocation, and the initial shock of the concentrated vapour may cause the patient to fall back insensible, and sudden death can result. Severe burning pain follows at once from the mouth to the stomach, and the patient retches, vomits, and has ammoniacal eructations. The abdomen becomes distended and tympanitic. The vomit may contain altered blood, is alkaline, and smells of ammonia. The breath smells of ammonia, the eyes smart, and sneezing and coughing occur.

The lips and tongue are swollen, and phonation is impaired. There

may be difficulty in breathing, and death from asphyxia may occur, generally coming on slowly but being steadily progressive.

The urine is scanty, generally alkaline, and may contain albumin and casts.

The general principles of treatment for the fixed alkalis apply here *Treatment* (see p. 75), but the respiratory condition also calls for relief. Inhalation of oxygen with carbon dioxide, tracheotomy, and artificial respiration may be necessary.

4.—SYNTHETIC ORGANIC SUBSTANCES

(1)—Acetylsalicylic Acid (Aspirin)

1495.] This is now probably the commonest drug taken by mankind, and in medicinal doses and even in doses definitely in excess it does little if any harm.

Acetylsalicylic acid, $C_6H_4(O.CO.CH_3).COOH$, being unstable readily *Physical properties* undergoes hydrolysis, especially in alkaline solution, to salicylic and acetic acids. An examination of the stomach contents in a case of poisoning by aspirin shows a mixture of aspirin, salicylic acid, and acetic acid, and the liver shows salicylic acid without any, or at most only traces of, aspirin. The decomposition of one acid into two in the body is important, for at least part of the symptoms are probably associated with acidosis.

Most cases of poisoning by aspirin are not fatal; recovery has followed *Fatal dose* a dose of 500 grains; 450 grains will probably prove fatal in some cases only, and occasionally quantities much less than this have been fatal in debilitated or seriously ill patients. In one case we recovered from the organs the equivalent of 184 grains of aspirin, but the amount taken was not known. It is very difficult to express an opinion, but we are inclined *Fatal period* to think that the fatal period is short in those cases which terminate in death. In the case cited above the deceased was observed to fall down in the street and, although he was taken by the ambulance to hospital within twenty minutes, he was dead on arrival.

The body shows dehydration. Usually a large dose of the poison has *Morbid anatomy* been taken in solid form or in thick suspension, and some undissolved traces should be found in the mouth or stomach. The stomach is small and rugous. The mucosa shows inflammatory reddening, with some petechial haemorrhage along the crests of the folds. In some cases the organ contains mucoid fluid and altered blood. The lungs are congested and oedematous, especially at the bases, where there are petechiae, which may also be seen in the epicardium. In the case cited above the heart's blood was fluid. There is general visceral congestion and marked parenchymatous degeneration of the liver and kidneys. Fatty degeneration of the liver may be a striking feature. The bladder is generally full. The urine, which should be carefully collected for analysis, is very acid and contains some albumin and granular casts. The brain is congested and slightly oedematous.

Symptoms

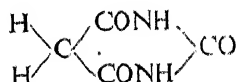
First, there is nausea with or without vomiting and tinnitus. Mental confusion and deafness follow, and later sleepiness or coma. The pulse-rate is somewhat raised, the breathing may be deep and slow, and the patient is pale and sweats profusely. The pressure of the cerebrospinal fluid has been recorded as raised and on examination contains salicylates. In most cases there is a gradual recovery with approaching convalescence in three days.

Treatment

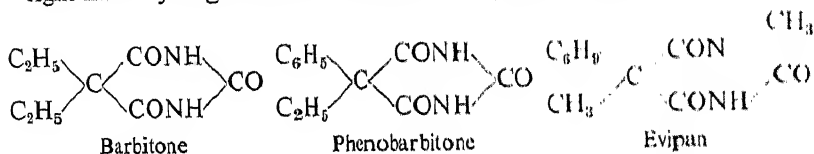
The stomach should be washed out with water (not alkali), and this should be repeated in a few hours. Several observers have recorded improvement after lumbar puncture and the removal of 30 c.c. of fluid; in severe cases, therefore, this would appear to be advisable and should be repeated if necessary. Purgatives and saline injections will assist in elimination of the drug. Although some workers deny that the more important aspect of the condition is that of acidosis, a diminution of the alkali of the blood has been observed, and acetone and acetoacetic acid have been found in the urine. It would therefore seem desirable to add sodium bicarbonate to the injected fluid, or buffered sodium lactate solution may be given intravenously (Williams and Panting). Daily examination of the urine for salicylate will be a guide to the completion of the elimination.

(2)—Cyclic Ureides and Barbituric Acid*Physical properties*

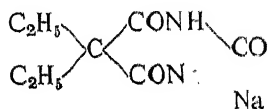
1496.] These drugs are described as cyclic ureides and are essentially compounds of malonic acid and urea; hence the alternative name of malonylurea. The simplest of the compounds, which, however, is not used in medicine, is barbituric acid itself or malonylurea. The formula is as follows:



By a process of substitution of other groups for the hydrogens directly attached to the carbon atom on the left an infinite number of compounds can be prepared, and by also substituting other groups for one of the right-hand hydrogens another series can be prepared, e.g.:



The introduction of sodium into one barbituric nucleus produces more soluble compounds, e.g.:



Soluble barbitone (veronal sodium or medinal)

The following is a list of most of the barbituric acid compounds at present (1939) on the market: *Barbituric acid compounds*

allobarbitone (dial), 5 : 5-diallylbarbituric acid
 allonal, which contains allylisopropylbarbituric acid
 amytal, isoamylethylbarbituric acid
 barbitone (veronal), 5 : 5-diethylbarbituric acid
 butobarbital (soneryl, neonal), butylethylbarbituric acid
 evipan, *N*-methyl-*C-C*-cyclohexenylmethylmalonylurea
 hebaral sodium, sodium *N*-hexylethylbarbiturate
 ipral, ethylisopropylbarbituric acid
 nembutal (pentobarbital sodium), sodium ethylmethylbutylbarbiturate
 noctal, isopropylbromopropanylbarbituric acid
 pernocton, sodium salt of secondary butyl- β -bromallylbarbituric acid
 phanodorm (cyclobarbital), cyclohexenylethylbarbituric acid
 phenobarbitone (gardenal, phenylbarbital, luminal), 5-phenyl-5-ethyl-barbituric acid
 prominal, *N*-methylethylphenylmalonylurea
 proponal, dipropylbarbituric acid
 rutonal, methylphenobarbitone
 sandoptal, isobutylallylbarbituric acid
 seconal, sodium propylmethylcarbonylallylbarbiturate.

Although we believe that the above list embraces all the substances of this group in use, these drugs masquerade under various names both in England and abroad. Thus barbitone (veronal) has for its aliases diethylmalonylurea, malonurea, barbitalum, malonal, hypnogen, and various other proprietary preparations, e.g. veramon, quadro-nox, veronigen, beatol, and chineonal, contain barbitone. Similarly phenobarbitone (luminal) may be described as acidum phenylaethylicobarbituricum, gardenal, luminal-natrium; and preparations such as theogardenal, theotone, theominal, alepsal, cafinal, optinoktin, salepsi, and lubrokal contain phenobarbitone with various other substances. Many of the barbiturates are also mixed with amidopyrine, a drug which should be used with the greatest caution; examples of these are allonal, veramon, veropyron, cibalgine, and optalidon.

It has been suggested that these drugs fall into two groups: (i) those which act for a shorter time with profound narcosis and a high degree of anaesthesia, death supervening from respiratory paralysis; and (ii) those which act for a longer time with low-grade narcosis, pulmonary congestion, and a greater liability to pneumonia. Nembutal, pernocton, amytal, and evipan belong to the first group, whereas phenobarbitone, allonal, and allobarbitone belong to the second.

Barbitone (veronal) 15 grains has been recorded as a fatal dose; this dose is extremely low in view of the fact that 5 to 10 grains is the medicinal dose. In general the average possibly fatal dose of this drug is about 50 grains. It may be said that, if the maximal medicinal dose of any *Fatal dose*

of these drugs is multiplied by 5, a general estimate of the possible fatal dose may be obtained.

Broadly speaking, these drugs when taken in toxic doses are associated with relatively long periods of coma before death ensues, as against morphine and chloral hydrate, with which the period of coma usually does not last more than twelve hours. The comatose period for the barbiturates may last several days or even a week.

Skin lesions, such as the large pemphigoid blisters, are not often seen at necropsy but should be looked for. There is some cyanosis of the head. The lungs are oedematous and heavy, and the air-passages contain frothy fluid. The oedema interferes with the aeration of the lungs, and the congested dependent postero-inferior parts (usually more markedly on one side) are plum-coloured, show resorption collapse, and sink *en masse* in water. The bronchi in these areas may contain pus, and, except when the period of unconsciousness was short and there was no rise of temperature before death, there are always slightly raised trefoil-shaped areas of broncho-pneumonia. Microscopically the oedema fluid shows an irregular sprinkling with red blood-corpuscles and polymorphonuclears. In the basal parts this may proceed to fibrinous consolidation. Pleural petechiae are almost always present and most frequent on the plum-coloured basal parts. There is little or no fluid in the pleural sacs.

The brain is congested and its substance slightly softened by oedema. There may be some flattening of the convolutions, but this is never pronounced, and subarachnoid fluid is always present in the sulci. There may be a slight 'pressure cone' (a ring on the under surface of the cerebellum round the medulla) but death is not due to mechanical compression but to toxic action on the vital centres of the medulla.

There is parenchymatous degeneration of the organs, which are flabby, slightly oedematous, and cloudy. The liver shows some fatty change. The bladder is generally full, and the urine should always be carefully collected. When a poisonous dose of a barbiturate with amidopyrine has been taken, e.g. allonal, the urine shows a characteristic red colour in acid solution, becoming purplish on the addition of solution of ammonia, due to the presence of a decomposition product of amidopyrine—rubazonic acid. So marked is the colour that a glance at the urine often gives a clue to the drug taken. It is stated that in cases of barbitone poisoning a false positive Wassermann reaction may be obtained.

A medicinal dose of a barbiturate produces a quiet easy sleep in about 30 minutes, which will last for 6 to 12 hours generally without after-effects. If the drug is taken regularly every night in medicinal doses, several effects may be noted; e.g. depression, visual hallucinations and even delusions, drowsiness, ptosis, diplopia, thickness of speech, tremors, and ataxy, which may be mistaken for drunkenness. Albuminuria and haematoporphyrinuria have been recorded, but in a series of 100 cases of poisoning we have never seen haematoporphyrinuria. The drugs are

quickly absorbed, partly decomposed in the body, and partly excreted in the urine, the amounts excreted varying considerably with different drugs. They are not cumulative, except when they are being taken regularly, when a fresh quantity taken before complete excretion of the previous dose may lead to a persistence of the above-mentioned symptoms for a few days. Addiction to these drugs is not common, but it occurs from time to time (Willcox).

When a toxic or possibly fatal dose is taken, the symptoms appear in a few minutes, the chief of them being headache, vertigo, and ataxy, without vomiting or abdominal pain. The patient falls asleep and can at first be roused with difficulty, but he soon becomes comatose. There may be a preliminary period of excitement with hallucinations for about twenty minutes. The coma when established is profound, muscles are flaccid, reflexes generally abolished, and all sensations and corneal reflex absent. There is often a persistent positive Babinski reaction. Breathing is stertorous and irregular and in the late stages may stop for a time and then start again. Cyanosis of a moderate degree is always present. The pupils are small but not pin-point and will react to light until the coma is deep, and in the terminal stages tend to dilate. Temperature is sub-normal, the body being cold and clammy and the pulse rather rapid and in the late stages feeble. There may be incontinence or retention of urine and incontinence of faeces. Although there is some diminution in the amount of urine excreted, it is not uncommon to find a distended bladder requiring catheterization. If an analysis to identify the poison is likely to be required, this first specimen is the most valuable and should always be retained in its entirety. The comatose state may last for several days.

Sooner or later, generally after the first 24 hours, there is a sudden rise of temperature up to 102° to 104° F., and an examination of the lungs shows the presence of broncho-pneumonia. This complication renders the prognosis much less favourable. Occasionally large blisters containing a clear fluid develop on various parts of the body.

As in all cases of narcotic poisoning, the stomach must be thoroughly washed out with water. On no account should sodium bicarbonate solution or any alkaline liquid be used, because it at once causes the drug to go into solution and to be increasingly rapidly absorbed. Cases have been described in which the coma noticeably deepened during lavage with a bicarbonate solution. Strong coffee, glucose, and a purgative should be left in the stomach. Since there is no chemical antidote to the barbiturates, the washing process should be repeated 4 hours later and again a third time. Analysis of the contents returned from the stomach has clearly demonstrated that the barbiturate is always found in all the washings. Colonic lavage should be performed also and repeated in 12 hours; the value of this has also been demonstrated by analysis. Shock should be combated by warmth and stimulants, e.g. digitalin and coramine together with full doses of strychnine hydrochloride $\frac{1}{4}$ grain every 4 hours. Oxygen with carbon dioxide should be

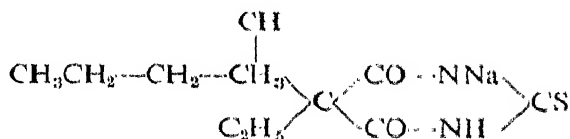
*Severe
symptoms*

Treatment

given if the cyanosis is considerable. The bladder must be watched and catheterized if necessary.

Lumbar puncture or, better still, cisternal puncture must be performed and as much fluid as possible drawn off. Since the fluid is under slight pressure, it is often possible to draw off 20 c.c. and upwards. This should be repeated at least every 12 hours until there are signs of returning consciousness; as many as six punctures have been made in some cases. The poison is invariably found in the cerebrospinal fluid. Finally the patient should be placed in bed with the head raised in view of the almost invariable onset of broncho-pneumonia. Some foreign workers recommend the use of very large doses of strychnine; 6 grains of strychnine have been given in a case of barbitone poisoning and followed by recovery. Picotoxin has also been recommended in large doses, but it is doubtful if the use of large doses of such powerful poisons is justified. Alcohol in large quantities has also been recommended; a woman who had taken 22 grains of phenobarbitone received by injection 20 c.c. of a 30 per cent solution of alcohol every 4 hours and recovered.

Recently there has appeared on the market a drug which is closely allied to the barbituric acid series but in which the terminal oxygen atom is replaced by a sulphur atom, i.e. sodium ethyl-1-methylbutylthio-barbiturate (pentothal sodium):



This may perhaps be the forerunner of a new series of drugs. Its use appears to be similar to that of evipan.

(3)—Straight-Chain Ureides: Carbromal Group

1497.] In addition to the above-mentioned derivatives of urea there are several drugs which may be called straight-chain ureides. Among these is the well known carbromal, perhaps best known under the name of adalin. Its formula is as follows:



These drugs in addition contain a bromine atom. Bromural (dormigene), another member, is α -monobromisovalerylurea.

There are but few fatal cases of poisoning by these drugs, because their toxicity compared with that of the barbiturates is low. Quantities as large as 300 grains have caused death, and smaller amounts may possibly be fatal. Recovery after 150 grains of bromural has been recorded.

It is impossible to make even an approximate estimate of the fatal period, but I have known death to occur in about thirty hours.

There are no characteristic signs at necropsy. After a possibly fatal dose of these drugs I have not been able to detect the drug in the tissues or in the urine. When organs, such as the liver and kidneys, and the urine are examined, it is possible only to detect considerable quantities of bromine, which although confirmatory does not establish the nature of the drug taken. Analysis of the stomach and contents or of stomach washings may, when the drug has not all been absorbed, reveal its true nature. *Morbid anatomy*

After a possibly fatal dose sleep passes into deep coma. At first the pulse is good and respiration normal, but as time passes, the pulse quickens and becomes feeble, the blood-pressure falls, and the respiration becomes shallow. All reflexes are absent. Pupils may be small and may for a time react. The condition appears to be one of myocardial failure, and life slowly ebbs away. Poisoning by these drugs does not produce broncho-pneumonia, the breathing is shallow, and cyanosis and an extensor plantar response are absent, whereas in poisoning by the barbituric acid group broncho-pneumonia always occurs except in those uncommon cases in which death is very rapid, there is some cyanosis, breathing is generally rather deep, and an extensor plantar response is present at all events until near the end. *Symptoms*

(4)—Chloral Hydrate and Allied Drugs

1498.] Chloral hydrate, butylchloral hydrate, chloralformamide, and chlorbutol are examples of substances which, although differing in constitution, produce in general a similar effect. Pure chloral, $\text{CCl}_3\cdot\text{CHO}$, is an oily liquid and is probably used only in the laboratory. The hydrate, $\text{CCl}_3\cdot\text{CH}(\text{OH})_2$, is a crystalline solid readily soluble in water. Although its poisonous effect resembles that of chloroform, its action is not due to the formation of chloroform in the blood-stream. Chloral hydrate is excreted in the urine mainly as urochloralic acid, a conjugated compound of chloral and glycuronic acid. *Physical properties*

Although 20 to 30 grains have on several occasions caused death, the average fatal dose must be put higher; 120 grains should be regarded as generally fatal to adults, and probably the small fatal doses recorded were associated with some cardiac disability (see below). *Fatal dose*

Death usually takes place in 6 to 10 hours. Cases in which death occurs rapidly are probably mainly in the aged or in those with cardiac disability, and in these patients relatively small doses rapidly cause death from cardiac failure. *Fatal period*

Death occurs in coma with cardiac and respiratory failure. The organs are congested and the extremities cyanosed. The brain is engorged and slightly swollen. The lungs are congested and may show considerable oedema, watery fluid filling the bronchi. The bladder is usually full. After a large dose there may be much inflammatory reddening of the upper food-passages. *Morbid anatomy*

When the drug was used more frequently, death was often due to accidental overdosage. This was especially liable to occur in patients

with cardiac disease and in addicts in whom fatty degeneration of the viscera was common.

The usual course is one of symptomless sleep passing on into coma and so to death, generally from respiratory failure. Vomiting may occur in the early stages, followed later by cyanosis, with slow irregular breathing, rapid irregular and weak pulse, paralysis and complete loss of sensation, with a subnormal temperature, very low levels being recorded, and a cold clammy skin. To the aged and to patients with cardiac affection chloral is very toxic, relatively small doses causing death rapidly from cardiac failure.

In chronic poisoning there are usually disturbance of digestion, diarrhoea, and loss of weight. Erythematous rashes and a superficial ulceration of the roots of the hairs of the head have been described. General depression, impairment of mental faculties, and a melancholic state occur. Sudden death is common among chloral hydrate addicts. Diagnosis is difficult in the absence of the knowledge that chloral hydrate has been taken.

The stomach should be washed out with water, and stimulants given, especially those acting on the respiratory centre, coffee *per rectum*, warmth, oxygen, and even artificial respiration in the late stages, and saline should be injected subcutaneously to assist elimination.

(5)—Sulphonal Group

1499.] Sulphonal, methylsulphonal (trional), and tetronal may be conveniently considered together. All these drugs are being less and less used; in fact it is doubtful if tetronal is now used at all. Sulphonal is diethylsulphonedimethylmethane, $(CH_3)_2C(SO_2.C_2H_5)_2$; methylsulphonal has one of the methyl groups, and tetronal both, replaced by an ethyl group. They are very sparingly soluble in water and therefore slowly absorbed and may take some hours to produce any effect. Owing to their very slow excretion these drugs possess a definite cumulative effect. They are pure hypnotics without any analgesic properties. Cases of poisoning by these drugs are rare nowadays; I have seen only one non-fatal case in eighteen years.

(a) Acute Poisoning

Death is reported to have occurred after taking 30 grains, and several deaths are recorded after taking 70 grains and upwards. Owing to the cumulative effect, deaths have been recorded from the daily use of 10 to 20 grains over a period of months. The fatal period varies from a few hours to several days.

There is no characteristic change at necropsy.

The symptoms vary; mental confusion, perhaps with excitement, convulsions, and ataxy are among the commonest. These are followed by stupor and unconsciousness. Later the patient becomes cyanosed, with a very weak pulse and irregular and stertorous respiration. Death is from respiratory failure. Red urine due to haematoporphyrinuria has

been recorded in anaemic women. When this occurs the prognosis is bad.

In those cases in which the drug is being taken regularly a break in the administration should occur every few days on account of its cumulative effect. *Treatment Prophylactic*

The stomach should be washed out immediately and four hours later. Purgatives and colonic washes should be given. Saline should be injected subcutaneously to assist in the elimination of the drug, especially if the period of unconsciousness has lasted several hours. Stimulants for the heart and respiration must be freely given. *Curative*

(b) *Chronic Poisoning*

The long-continued use of these drugs is stated to cause headache, vomiting, gastritis, constipation, albuminuria, and haematoporphyria. Various skin eruptions have also been described.

(6)—Hydrocyanic Acid

(*Synonym.*—Prussic acid)

1500.] This acid is found in small quantities in many plants in combination generally as a glycoside, and when the plant is disintegrated the acid may be generated. Such plant preparations are occasionally used in medicine, e.g. *Prunus serotina* (Virginian prune bark). Dilute hydrocyanic acid, B.P., is a 2 per cent solution, and stronger hydrocyanic acid (Scheele's acid), which is a 4 per cent solution, is occasionally used. The pure acid is rarely seen outside the laboratory. All solutions of the acid give off fumes of the acid very readily; even dilute solutions must therefore be handled with caution. The salts of hydrocyanic acid, chiefly those of potassium and sodium, are widely used in photography, electroplating industries, and in the extraction of gold from mineral ores. The salts of zinc and mercury are used to impregnate medical gauze. In view of the wide-spread use of the acid in gaseous form for the fumigation of greenhouses, ships, and houses infested with bugs it is necessary to issue a warning with regard to adequate ventilation of the premises before permitting any one to enter after fumigation. Several fatalities have occurred in this way. Recently the Home Office have made regulations under the Hydrogen Cyanide (Fumigation) Act, 1937 (Statutory Rules and Orders 1938 No. 1578). Articles such as bedding should be thoroughly and separately exposed to the air. When one of a row of houses is being disinfected, the fumes may leak through faults in the brickwork with fatal results.

The acid and its solution are colourless liquids with a characteristic odour of bitter almond. They are unstable and decompose readily. *Physical properties*

The cyanides of potassium and sodium are generally seen in powder or in lumps, and when pure are almost colourless. They are deliquescent and dissolve readily in water. Their solutions are strongly alkaline and when swallowed produce in the stomach evidence of corrosive alkaline poisoning. *Cyanides*

In addition to the simple cyanides there are a number of complex cyanides, most of which are not poisonous. Potassium ferrocyanide $K_4Fe(CN)_6$, potassium ferricyanide $K_3Fe(CN)_6$, potassium sulphocyanide (thiocyanate) $KCNS$, ammonium sulphocyanide (thiocyanate) NH_4CNS , and potassium cyanate $KCNO$ are among them. Death has occurred after taking $3\frac{1}{2}$ ounces of potassium sulphocyanide and recovery after 1 ounce. The ferrocyanides may cause death, for when treated with sulphuric acid of about 10 per cent strength they liberate hydrocyanic acid, which may be inhaled. On the other hand, cyanogen C_2N_2 , cyanogen chloride $CNCl$, and cyanogen iodide CNI are very poisonous but are only met with in the laboratory or the factory. The well known sodium nitroprusside $Na_2Fe(CN)_5(NO) \cdot 2H_2O$ is also highly poisonous.

A quantity of a solution of hydrocyanic acid equivalent to $\frac{1}{16}$ grain of pure hydrocyanic acid has caused death. Thus it may generally be considered that about 1 grain, the equivalent of 55 minims of dilute hydrocyanic acid B.P., is a possibly fatal dose; 2.4 grains of the potassium salt have also caused death, and 5 grains have often done so. Recovery has occurred after much larger doses.

Hydrocyanic acid is the most rapidly acting poison known, death generally occurring in 2 to 10 minutes. If the patient lives for 30 minutes, recovery is likely, although death has been known to occur after several hours.

At necropsy the body externally is bright and life-like. Hypostasis, instead of having the usual slaty colour, is of a bright reddish-violet colour. There may be froth round the mouth, the eyes are open and staring, the cornea glassy, and the pupils dilated. On opening the body there is often a smell of bitter almond. In all cases in which cyanide is suspected the organs to be sent for analysis should be placed with the least delay into tightly sealed glass jars on account of the volatility of the poison. The mode of death must be borne in mind when deciding what organs to reserve for analysis. Thus, although the stomach and its contents and the liver should be reserved when the poison is taken by the mouth, the lungs and as much blood as can be obtained must be reserved when the poison has been inhaled. The blood, both in the arteries and in the veins, is liquid and bright pink, and this colour is noticeable in the general musculature of the body. So striking is this feature that on many occasions the condition has been mistaken for carbon monoxide poisoning; therefore, unless care is taken, in the absence of material facts a wrong deduction may be made. The mucous membrane of the stomach shows reddening when hydrocyanic acid has been taken, but, if potassium cyanide or sodium cyanide has been taken, it resembles that seen in moderately severe poisoning due to a corrosive alkali. All samples of cyanide contain some free alkali and many commercial samples a considerable quantity of potassium carbonate or sodium carbonate in addition, with the result that when cyanides have been taken there is an added factor in the appearance of the stomach. The

stomach contents will generally be alkaline when these salts have been taken.

Symptoms occur generally in a few seconds but are occasionally delayed for a minute or two. During this later period the patient may perform a few acts, such as washing out the glass and putting the bottle away, which accounts sometimes for the absence of evidence of how the poison was administered and at first sight suggests homicide. In animals a cry heralds the unconsciousness, but this seldom occurs in man. During unconsciousness the respirations are rapid and vigorous at first, soon becoming slow and gasping. General convulsions often occur, but these may be confined to groups of muscles, e.g. trismus. Soon the paralytic stage is reached, in which the patient is flaccid, the reflexes are abolished, the eyes are open and staring, with pupils dilated and fixed, and the skin is clammy with cold perspiration. The mouth may be covered with froth, which may be blood-stained, and an odour of bitter almond may give a clue to the nature of the poison. The pulse is rapid and so weak as to be impalpable. Respirations become more feeble and finally stop, the heart beating for a short time after the respirations have ceased. *Symptoms*

In the few cases of recovery the unconsciousness persists for several hours and eventually the patient awakes and is but little the worse for his experience. Recovered patients have told of a desire to vomit and of constriction of the chest with a terrible feeling of impending suffocation. *Recovery*

Cases of poisoning occur from time to time from inhalation of the gaseous form. The chief symptoms are a sense of constriction in the chest, giddiness, confusion, palpitation, and unconsciousness. The salts *Poisoning by inhalation*

of hydrocyanic acid act in a similar manner to solutions of the acid and cases of poisoning by the salts are far commoner. In addition to the symptoms described above there may be a sense of constriction in the throat, with a burning pain, and perhaps vomiting, owing to the corrosive action of the salts. Should recovery occur, convalescence will be delayed owing to the caustic alkaline action on the throat and stomach. *By salts*

Cyanides, probably like almost every other poison, may produce a tolerance in workers regularly handling them; it is stated that those working with it regularly in the gold mines are unaffected by relatively large quantities. On the other hand, headache, vertigo, pallor, loss of appetite, and respiratory embarrassment have been described in employees in cyanide works. *Tolerance to cyanides*

In the vast majority of cases the effects of the poison are so rapid that, even if he reaches the scene before death, the practitioner has no time to do anything for his patient. If time permits, washing out the stomach with water containing some sodium thiosulphate (photographic hypo) is probably the best measure, and some of the salt should be injected intravenously in 10 per cent solution. By this means the toxic cyanide may be converted into the non-toxic thiocyanate. Stimulants, warmth, faradization and, especially, artificial respiration have in a few instances assisted in saving life. It is stated that cobaltous nitrate, either *Treatment*

by mouth or intravenously, is of value, or a mixture of ferrous sulphate, ferric chloride, and potassium carbonate may be given by the mouth. Although such chemicals are not likely to be available in such an emergency, factories and works where cyanide is in regular use might consider the desirability of having them available.

(7)—Metacetaldehyde

(*Synonyms*.—Meta; metaldhyde)

1501.] This is a polymeride of acetaldehyde having a formula $(CH_3CHO)_n$. It is a white crystalline substance and is manufactured in sticks. It is used as a convenient substitute for methylated spirit for heating purposes. It has been recommended as a slug-killer for gardens, for which purpose it is powdered and mixed with bran. In the form of sticks it has a not unattractive appearance, and when powdered closely resembles sugar; its taste, though not very interesting, is not unpleasant. It is therefore not surprising that it has been eaten by children in a number of cases. Since it is also poisonous to animals, it should be used in the garden with caution. It has been used for the purpose of suicide.

Its action is due to meta itself and not to its decomposition into acetaldehyde.

In one fatal adult case the deceased had in all probability taken 6 to 10 sticks, i.e. 360 to 600 grains. Two cases have been recorded in which the eating of 6 sticks by adults was followed by recovery. In dogs a quantity of 0.6 gram per kilo of body-weight is stated to be fatal. In a fatal case death generally occurs in 1 to 3 days.

There are no characteristic signs at necropsy. Petit and Audistère stated that in animals poisoned with meta the urine gave a red colour with Denigés' reagent (guaiacol and sulphuric acid). If this is true also in man, such a reaction will prove of great assistance in the diagnosis of poisoning by this substance.

As meta is very insoluble in water, the onset of symptoms is delayed. The onset also depends on whether the substance is swallowed in small lumps or in a powder, the latter causing the earlier onset of symptoms. Generally in about 2 to 3 hours vomiting occurs of meta mixed with food. If vomiting is absent, the symptoms may be delayed for a few hours longer. The next symptom is tremor of the upper limbs with flushing, restlessness, and delirium. The tremors are followed by severe cramps and convulsions, which in bad cases may be epileptiform. The patient is stuporose, with amnesia and a staggering gait. He slowly becomes unconscious and, in severe cases, comatose. There is no disturbance of reflexes or of the heart's action, and Kernig's sign is absent. In a mild case the tremors and cramps are limited to the arms and pass off in 24 hours. In serious cases the cramps are rapidly followed by generalized epileptiform convulsions. These are followed by coma which may last 3 to 4 days with recovery or death.

The prognosis depends on the rapidity of the appearance of symptoms, the increasing or decreasing severity of convulsions, and the rapidity of

the appearance of coma. In animals the blood urea is stated to be raised. Most patients recover; in a series of twenty-four cases collected by me there were six deaths.

The stomach should be washed out with water several times. This *Treatment* should be repeated in a few hours, and purgatives should be administered. It is stated that in animals the alkali reserve is diminished; consequently the administration of alkalis would seem to be indicated. Further treatment should be symptomatic.

(8)—Nitrobenzene

(*Synonyms*.—Oil of mirbane; imitation oil of bitter almond)

1502.] Nitrobenzene, $C_6H_5NO_2$, is extensively used in perfumery and as a flavouring agent, being a cheap substitute for oil of bitter almond. It is also used as an ingredient of shoe dyes and floor polishes and is an important intermediary in the aniline dye industry.

Nitrobenzene is a blood poison, the red cells becoming haemolysed *Action* and the circulating haemoglobin converted into methaemoglobin. It also acts on the central nervous system, stimulating and afterwards paralysing it.

On several occasions 15 to 25 drops have proved fatal, especially if *Fatal dose* the poison is taken with alcohol as an abortifacient. Recovery has followed very large doses, i.e. quantities greater than 1 ounce. Death has taken place from inhalation and absorption through the skin.

Death is probable in about 7 hours, but it has occurred in 1 hour to *Fatal period* 24 hours.

At necropsy the external appearances vary. In the acute cases the face *Morbid anatomy* may be flushed, with livid lips and blue nails. If the patient has lived some hours, there may be pronounced cyanosis. The organs smell of bitter almond, a very persistent and characteristic odour which must not be mistaken for hydrocyanic acid. The stomach shows a brilliant reddish congestion with submucous haemorrhages. The blood may be dark and viscid and show the spectrum of methaemoglobin, but the post-mortem presence of this spectrum must be accepted with caution if much delay has occurred between death and the necropsy. The urine may contain amino-bodies derived from the nitrobenzene, and these reduce Fehling's solution.

The symptoms present very different features which largely depend *Symptoms* on the acuteness of the poisoning. When a poisonous dose is taken, especially with alcohol, a burning sensation in the mouth and throat is followed by numbness and tingling. There may or may not be vomiting. Soon pallor appears, followed by lividity; unconsciousness occurs with great rapidity, perhaps in twenty minutes, and death from respiratory failure occurs in an hour or two.

In less acute cases the onset of symptoms may be delayed for an hour or more. The face is pale, the nails are bluish, and there are ataxy, vomiting, and eventually coma. Muscular twitchings, trismus, and involuntary evacuation of urine and faeces may occur. The patient is

generally deeply cyanosed, and the blood on examination is dark and viscid and will sooner or later show the spectrum of methaemoglobin (see Vol. II, Plate VI, facing p. 499). Death occurs in coma, or recovery takes place after a variable period of unconsciousness. In a few days, however, nausea and vomiting may commence again, with perhaps a rise of temperature and the appearance of toxic jaundice.

The blood picture is that of anaemia with granular degeneration of the red cells, alteration of size and form, and later the presence of nucleated red cells. The vomit and the urine in the early stages smell of nitrobenzene.

The stomach should be washed out with water repeatedly until the returned fluid no longer smells of nitrobenzene. Purgatives should be given. Oily substances and alcohol should be avoided. If there is reason to believe that the lysis of red cells is extensive, a blood transfusion may be considered.

For chronic poisoning see page 173.

(9)—Oxalic Acid

1503.] This acid, $(\text{COOH})_2 \cdot 2\text{H}_2\text{O}$, is a colourless crystalline non-deliquescent substance and, owing to its close physical resemblance to magnesium sulphate, cases of poisoning have occurred from mistaking the acid for Epsom salts.

It is widely distributed in the vegetable kingdom but rarely in sufficient quantity in edible plants to cause symptoms (see OXALURIA, Vol. IX, p. 344); in these conditions the acid is combined as the calcium salt. The acid is commonly used in households for cleansing and bleaching, and in industry in many processes.

Potassium binoxalate, $\text{KHC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$, is a colourless crystalline substance resembling the acid. It is not used much outside the laboratory or the factory.

Potassium quadroxalate, $\text{KHC}_2\text{O}_4 \cdot \text{H}_2\text{C}_2\text{O}_4$ (*synonyms*, salts of lemon; salts of sorrel), is met with more commonly than the acid in the household and is used for similar purposes. A colourless crystalline substance, it has also been mistaken for Epsom salts.

The action and effects of the acid and its salts are so similar that for purposes of discussion they are considered together.

Although 60 grains have caused death, probably $\frac{1}{2}$ to 1 ounce may be regarded as an average fatal dose. Recovery has occurred after 2 ounces.

Death has taken place in a few minutes and often occurs within an hour or two. A few cases may last twenty-four hours and even some days, but, if the twenty-four hour period is passed, recovery is likely.

The corrosive effects are less severe than those of the strong mineral acids. Not only is oxalic acid less intense in this respect, but it also has less time in which to act, most of the fatal cases terminating within two hours. As with the other corrosive agents, many of the changes take place after death. The mucosa of the mouth, pharynx, and oesophagus may be white and opaque or reddened and in places slightly swollen.

The oesophagus is contracted. In the stomach the changes are more severe, although even here, if the acid is dilute, the changes may be very slight. Usually the gastric mucosa is uniformly reddened and corrugated. After a concentrated dose the surface is sometimes blackened, as in poisoning by hydrochloric acid. This may happen even when death has occurred in a matter of minutes. Perforation is rare. The stomach contains a mucoid fluid mixed with altered blood. Oxalic acid interferes with clotting, and haemorrhage from the injured gastric surface is freer than in poisoning by the strong acids, which cause a styptic necrosis of haemorrhagic tissue. The small intestine may be affected for a short distance. *Stomach*

In the kidneys a striking effect, when present, is a precipitation of calcium oxalate in the tubules. This is observable microscopically as a whitish line in the intermediate zone. The characteristic tetrahedra are uncommon in this situation, but are present in the acid urine, which also contains albumin and possibly some red blood-corpuscles and casts. *Kidneys*

Oxalic acid and its salts have two distinct actions: local and systemic. When a relatively small dose is taken in a dilute solution, the symptoms and signs of the local action may be negligible and only those of its systemic action become manifest. *Symptoms*

When a quantity of the poison is taken, a sour taste is experienced with a burning pain from the mouth to the stomach and radiating over the abdomen. Thirst is intense, swallowing is difficult, and retching and vomiting of bright or dark blood occur. Collapse and shock soon become manifest. The voice is faint and husky, and soon there is aphonia. The mouth and throat are whitened, and the mucous membrane is necrosed but not so readily detachable as in poisoning by mineral acids, and the vomit does not usually contain shreds of tissue. The vomiting varies in severity and may even be absent. *Local action*

Soon after the absorption of oxalic acid the patient is pale with an anxious expression, the skin is bathed in cold clammy perspiration, the pupils are contracted, there are a general numbness, tingling, and cramps in the extremities, and the patient often complains of shooting pains from the lumbar region down the legs. Respiration is rapid and laboured, there may be convulsions, coma supervenes, and death soon follows. *Systemic action*

Death is the result mainly of the poisonous effects after absorption. The calcium content of the blood is reduced sufficiently to prevent post-mortem coagulation.

It is generally safe to wash out the stomach, and, since this form of treatment is far more efficient than emetics in eliminating the poison, it is only in those cases in which it is believed that a very highly concentrated dose has been taken that there should be any hesitation. Since so many cases terminate fatally in a very short time, it is obviously important to remove the poison as completely as possible. The stomach should be washed out with saccharated solution of calcium hydroxide, which not only neutralizes the poison but also converts it into an *Treatment*

insoluble oxalate. After several wash-outs a quantity of the lime-water should be left in the stomach. In most cases of poisoning in which the stomach-tube is permissible it is desirable to wash a second time a few hours later, because many poisons after absorption are re-excreted into the stomach.

If the patient survives for an hour or two, there is a good chance of recovery; therefore every use of eliminative processes should be made. As diarrhoea is common in this form of poisoning, colonic lavage may not be necessary, but, unless the diarrhoea sets in soon, this should be done.

(10)—Paraldehyde

Physical properties

1504.] This substance, a mixture of polymerides of acetaldehyde, with the formula $(\text{CH}_3\text{CHO})_3$, is a colourless liquid with a burning taste and a characteristic smell. Its action is similar to that of chloral hydrate.

(a) *Acute Poisoning*

Fatal dose and fatal period

Its toxicity is low, and it is difficult to give any figure which may be regarded as a possible fatal dose. Probably several fluid ounces would have to be taken. It is impossible to define the fatal period.

Morbil anatomy

Apart from some reddening of the stomach wall, which depends on the time that the patient has lived after taking the poison, and a characteristic odour of the drug in the viscera, there is nothing characteristic at necropsy.

Symptoms

Large doses may cause nausea, vomiting, and dizziness. The patient soon passes into stupor and unconsciousness with complete muscular relaxation, followed by recovery or by death. The condition should be easily recognized, because even after medicinal doses the characteristic odour of the drug is noticeable.

Treatment

The treatment used in most narcotic drug poisoning may here be followed, in particular that applied to sulphonal (see p. 85).

(b) *Chronic Poisoning*

Many persons have become addicts to this drug despite its unpleasant odour and taste; it is alleged that it produces a definite euphoria. The symptoms are disturbances of digestion, emaciation, and muscular weakness with tremor. Mental degeneration ensues, with loss of memory, confusion, hallucinations, and delusions. In such cases it is not uncommon for persons to take 2 to 3 fluid ounces of the drug daily.

(11)—Phenol and Lysol

1505.] Phenol when pure is a colourless crystalline deliquescent solid. It liquefies when water is added in the proportion of 100 parts of phenol to 10 of water, forming 'liquefied' phenol, and remains liquid until 30 to 40 parts of water are added, when the liquid separates into two layers, the upper layer consisting of a solution of water in phenol and the lower of a solution of phenol in water. When sufficient water is added so that

the ratio of phenol to water is 1 to 13 the phenol passes completely into solution and remains in solution in all dilutions above this ratio.

The cresols are only slightly soluble in water, a saturated solution being about 2 per cent. They are commonly used as antiseptics, e.g. solution of cresol with soap (lysol). In this form the cresol is miscible in all proportions with water, alcohol, and ether, and no precipitation should occur even with hard water. This disinfectant is prepared by heating cresol with oil (generally linseed) and potassium hydroxide. The resultant liquid is soapy to the touch and contains a small amount of free alkali. The standard proportion of cresol in lysol is 50 per cent. *Cresols*

In several cases 60 grains of phenol have caused death, but recovery has occurred from much larger doses. The concentration of the poison when taken is also an important factor. Death has followed local application to wounds and its use as a douche. It may be assumed that the toxicity of the mixed cresols is the same as that of phenol, but the low solubility of the former may be a favourable factor. It is, however, unlikely that the pure cresols would be taken, because they are not available to the public. Lysol, the common form available to the public, is completely miscible with water; its toxicity may therefore be regarded as similar to that of phenol. Although exceptional, a fatal case of lysol poisoning is recorded after taking 1 to 2 teaspoonfuls of lysol. If the higher figure is taken and the lysol assumed to be 50 per cent cresol, this is equivalent to 60 grains of mixed cresols. The degree of dilution here also is of importance. Recoveries after 3 fluid ounces and upwards are known. Generally speaking, the average fatal dose of both phenol and lysol (in terms of the cresol) is probably greater than 60 grains and is commonly stated to be about $\frac{1}{2}$ fluid ounce. *Fatal dose*

Although deaths, about 30 minutes to several days after the poison was taken, are on record, in most fatal cases death probably occurs in 2 to 8 hours. One fatal case is recorded in which a man carrying a bottle of lysol in his hip-pocket went to sleep, the bottle broke, and his skin was brought into contact with the lysol over an area extending from hip to heel on one side. He died in 30 to 45 minutes. *Fatal period*

Brownish or white eschars may be present about the mouth from dribbling of the poison when taken. In the bucco-pharynx and oesophagus (at the lower end and where it crosses the left bronchus) the surface is stiffened and white, owing to the tanning effect of the poison, and the deeper tissues are loose and translucent from inflammatory oedema. The stomach is contracted, rugous, and stiff, like a formalin-fixed specimen. The coagulated surface, which is brown from alteration of blood in the congested capillary bed, may be broken up and fissured by the muscular movements of the organ during life. The changes are generally most pronounced along the crests of the folds, where the mucosa is most exposed. The contents of the stomach are watery, generally smell strongly of the poison, and often contain blood. They are acid when phenol has been taken but are generally alkaline in lysol poisoning, because lysol contains some free alkali. In places there *Morbid anatomy*
Stomach

may be a little coagulated mucus and adherent fibrin; sometimes the coagulation extends through the wall of the stomach to the adjacent intestine. The poisonous effects do not pass far into the small intestine. The transverse folds of the duodenum may show the same brown fixation-necrosis as the stomach. In the lungs there may be focal necroses due to aspiration of the poison during swallowing or vomiting, but hypostatic congestion and, if the patient has survived long enough, broncho-pneumonia are commoner. There is often tubular nephritis. The urine contains casts and may smell of the poison. The smell may also be detectable in the viscera, which show general congestion and parenchymatous degeneration. The contraction of the pupils seen in coma is absent.

Symptoms When the poison has been taken by the mouth, there is an immediate hot burning sensation from the lips to the stomach. This is soon dulled, owing to the local anaesthetic effect. Vomiting generally, but not always, occurs and for the same reason is not very pronounced. In many cases of poisoning the contact of the poison with the lips produces local damage, the lips and angles of the mouth being stained brown and the buccal mucous membrane whitened. Poison trickling down from the mouth may also produce a brownish stain. The patient is collapsed, with a feeble pulse, and soon passes into coma, often preceded by mental symptoms, such as delirium and convulsions. The pupils are contracted, the surface of the body is cold and clammy, and the temperature is subnormal. Occasionally, if the patient lives long enough, there may be hyperpyrexia. Death may occur from cardiac paralysis or from pulmonary oedema. A diagnosis may be made from the odour of the breath. If concentrated poison has been taken, the vomit contains shreds of mucous membrane and altered blood. The urine is of normal colour, but it darkens on being allowed to stand in contact with air (carboluria). This change is due to hydroquinol or pyrocatechol substances formed in the body from the poison. The urine may also contain albumin, casts, and even blood, and, if the acute phase is recovered from, the patient may die later from uraemia. Jaundice has also been observed as a sequel. When the poisoning has resulted from absorption through the skin or the vagina, the general symptoms are similar.

Treatment The stomach should be washed out with copious quantities of water, especially since the common emetics, even apomorphine hydrochloride, may fail to produce emesis. Saccharated solution of calcium hydroxide (lime-water) may be added to the water used for lavage. When lavage is completed, a quantity of magnesium or sodium sulphate may be left in the stomach in the hope that the poison in the liver may be converted into the innocuous sulphonic acid derivative, but, owing to the prevalent view that sulphates are not absorbed, it has been suggested that these drugs should be given intravenously. Demulcent drinks, excluding those containing oil, may be given. The shock must be combated, and stimulants will be required. Otherwise the treatment is symptomatic.

In cases of chronic poisoning there are carboluria and possibly the *Chronic poisoning*
post-mortem appearances of ochronosis.

5.—ALKALOIDS

(1)—Aconitine

1506.] Aconitine and allied alkaloids are the poisonous active principles *Sources*
of *Aconitum napellus*, commonly grown in English gardens. There are
several other species of this genus, most of which contain these alkaloids.
The alkaloids are present in all parts of the plant, although only the
root is official in the British Pharmacopoeia. No dose of the plant or of
the alkaloid is given in the Pharmacopoeia, and it is now generally used
to prepare a liniment. The root has been mistaken for horse-radish with
fatal results.

Aconitine is one of the most powerful poisons known. As little as *Fatal dose*
 $\frac{1}{30}$ grain has proved fatal.

Death occurs generally in 3 to 4 hours, although both shorter and *Fatal period*
longer periods are known.

When toxic quantities are taken, numbness and tingling of the mouth *Symptoms*
and tongue are felt in a few minutes, followed by a burning sensation
down the throat and in the abdomen. There is a profuse salivation, and
there may be vomiting. The numbness and tingling soon spread over
the skin and are particularly noticeable in the extremities. Pains in the
eyes and head and a difficulty in swallowing are experienced. The pulse
is slow, feeble, and irregular, and symptoms of collapse appear. Respiration
is slow and laboured, and there is muscular weakness. The patient
feels cold, and the skin is clammy. Muscular twitchings often occur and
may be followed by convulsions. The pupils in the late stages are dilated,
and the intellect is clear to the end. According to one writer the pricking
of the throat and skin is almost pathognomonic, the only other poison
which produces similar effects being veratrine.

Death takes place from either respiratory or cardiac paralysis, the
former being commoner.

Treatment consists of gastric lavage with charcoal suspension or with *Treatment*
tannic acid solution and the administration of stimulants, the choice
depending on whether the respiratory or the cardiac functions appear
to be the most involved. The use of oxygen may be desirable, and warmth
is necessary.

(2)—Atropine Group

1507.] The more important solanaceous plants from which this group of *Sources*
alkaloids is derived are: *Atropa belladonna*, which contains *l*-hyoscyamine with a small amount of atropine; *Hyoscyamus niger*, which
contains *l*-hyoscyamine with a small amount of *l*-hyoscyne; *Datura*
stramonium, which contains chiefly *l*-hyoscyamine with some atropine;
and *Datura metel*, which contains *l*-hyoscyne with some atropine. The
first three of these grow in England but are not common; consequently
poisoning from eating portions of the plants is rare. The woody night-

shade, *Solanum dulcamara*, is often mistaken for *Atropa belladonna* but is not poisonous or only slightly so. Many other solanaceous plants contain these alkaloids.

The three chief alkaloids of these solanaceous plants are atropine, hyoscyamine, and hyoscine (scopolamine).

Atropine Atropine is racemic hyoscyamine, i.e. it contains equal quantities of laevo-rotatory and dextro-rotatory hyoscyamine. The laevo-rotatory form is active medicinally, whereas the dextro-rotatory form is only slightly active.

Hyoscyamine Hyoscyamine as found in plants is a pure laevo-rotatory hyoscyamine, but it is easily converted into the racemic form, e.g. by the action of dilute alkali.

Hyoscine Hyoscine (scopolamine) is a closely related laevo-rotatory alkaloid with a slightly different chemical structure. The alternative name for hyoscine is due to the fact that a considerable quantity of the pure alkaloid used in medicine is derived from another member of this group of plants, *Scopolia carniolica*.

The poisonous actions of these alkaloids are so far similar that they may be discussed together. It will, however, be understood that in cases of poisoning due to extracts of plants in which a mixture of alkaloids occurs the symptoms may vary and it may be impossible to differentiate the effects.

Fatal dose Individual response to these drugs varies so much that it is very difficult to fix even approximately an average fatal dose; further, in most cases the poisoning has been followed by recovery. It is probable, however, that $\frac{1}{2}$ grain of the pure alkaloid or the corresponding amount of the crude drug may be regarded as fatal. Examination of the recorded cases shows that quantities greater than this amount have sometimes proved fatal and have sometimes been recovered from. Death generally

Fatal period takes place within twenty-four hours from the time when the drug was taken.

Symptoms After a toxic dose there is soon a marked dryness of the mouth and tongue due to the inhibition of the flow of saliva. Swallowing is difficult, thirst acute, and the voice hoarse. The pupils become widely dilated and vision indistinct. The skin is flushed and dry, and in the later stages eruptions, generally morbilliform, have been described. In some cases nausea and vomiting occur, and headache and giddiness are often present. Respiration is quickened, and there is a rapid bounding pulse. The patient is generally excited, talkative, and restless, and may pass on to a maniacal delirium, and later there may be muscular twitchings leading to general convulsions. The flow of urine is generally diminished. Later, signs of paralysis appear, the stage of excitement passing to quiet, then sleep, then coma. At this stage respiration and pulse are slow, with weakening and irregularity, and finally death occurs from respiratory failure. It is stated that in those who have recovered the mind is a complete blank from the time when the poison was taken until convalescence. In convalescence the patient is often confused

for a day or two, and the dilatation of the pupils remains for several days.

Stomach and colon should be washed out as indicated on page 100. *Treatment*

In the earlier stages of the illness, in the stage of excitement, depressants are required but, owing to the ultimate action of this poison, drugs which depress the respiratory centre must be avoided. Thus, although often recommended, morphine should be avoided and one of the barbiturates may be used instead. When convulsions are severe, it may be necessary to use ether or chloroform for a time. *Earlier stages*

In the later stages, when paralysis is manifest, stimulants, especially those which act on the respiratory centre, are required. *Later stages*

(3)—Cocaine and its Substitutes

1508.] Fatal accidents due to cocaine used as a local anaesthetic have led to the production of many so-called cocaine substitutes, which must be assumed to have an action similar to that of cocaine, although many differences in detail will be manifest.

The alkaloid cocaine occurs in the leaves of *Erythroxylum coca*. The leaves contain several alkaloids, of which cocaine alone is official in the British Pharmacopoeia. Cocaine may also be prepared synthetically from ecgonine. Cocaine, ecgonine, and their salts and esters are included in the drugs controlled by the Dangerous Drugs Act (see Vol. X, p. 7).

The effects on persons unaccustomed to the drug vary greatly; it is therefore very difficult to state even approximately a fatal dose. Death has resulted from the application of as little as $\frac{2}{5}$ grain to the conjunctiva, and $\frac{1}{2}$ to $1\frac{1}{2}$ grains applied locally to mucous membranes or raw surfaces and by injection have several times caused death. On the other hand, quantities in excess of these amounts have often been used without producing symptoms. Probably about 15 grains would in most instances cause death. *Fatal dose*

Death usually occurs in about half an hour, and if the patient survives this time he will probably recover. Nevertheless the fatal period has been prolonged as long as four hours. *Fatal period*

There are no characteristic signs at necropsy, but the organs are usually congested. Marks caused by a hypodermic needle should be looked for, and, if the patient was a cocaine addict, special attention should be paid to the nasal septum, which may be damaged or perforated from taking the drug as 'snuff'. *Morbid anatomy*

When an analysis is required and puncture marks are found, the area of skin and tissues in the region should be widely excised and examined for the presence of cocaine. This statement applies generally to medication by injection.

When a toxic dose is taken, either by mouth or by injection or by local application, the symptoms arise quickly but vary considerably. Generally the patient is restless, excitable, and talkative, often making foolish incoherent remarks. This condition may progress to delirium and even mania. Numbness and tingling, with or without anaesthesia, are noted *Symptoms*

in the extremities. The pulse is accelerated at first but later is weak and irregular. Respiration is at first shallow. The pupils are generally dilated and insensible to light. Clonic or tonic convulsions may occur, and the patient ultimately passes into coma, death being due to respiratory failure. Instead of the preliminary symptoms of excitation, the patient may be calm and wish to sleep.

Treatment

The stomach should be washed out with potassium permanganate solution with adsorbent charcoal suspension. Stimulants, e.g. ammonium carbonate, are required, and warmth and oxygen if the respiration is embarrassed.

(4)—Colchicum

1509.] *Colchicum autumnale* contains the alkaloid colchicine, of which probably about $\frac{1}{3}$ grain may cause death in a variable period within twenty-four hours. The symptoms are those of irritation: vomiting, diarrhoea, and prostration. Anuria and haematuria have been recorded. The treatment is to wash out the stomach with tannic acid solution or with adsorbent charcoal suspension and to give mucilaginous drinks and stimulants. The post-mortem signs are those of gastro-intestinal irritation with congestion of the kidneys and perhaps evidence of a toxic nephritis.

(5)—Conium

1510.] *Conium maculatum* (hemlock) contains the alkaloid conine, an oily liquid of which one to two drops ($\frac{3}{4}$ to $1\frac{1}{2}$ grains) are considered to be a fatal dose. It acts rapidly, death usually occurring in three hours. The symptoms are burning of mouth and throat, drowsiness, muscular weakness, and a staggering gait. Death is due to respiratory failure. The treatment is gastric lavage and stimulation of respiration. At necropsy there is nothing characteristic, apart from signs of asphyxia.

(6)—Gelsemium

1511.] The chief alkaloids of *Gelsemium sempervirens* are gelsemine and a mixture of alkaloids called gelseminine, of which the former is the more important. The fatal dose and period are uncertain. The symptoms of poisoning are muscular weakness, general prostration, diplopia, dilatation of the pupil, and slow pulse. Death is due to respiratory failure. The treatment is to wash out the stomach, to give stimulants, and to keep the patient warm. No characteristic sign is found at necropsy.

(7)—Ipecacuanha

1512.] The chief alkaloids of this plant are emetine and cephaeline. Owing to its emetic properties it is doubtful if a case of poisoning by ipecacuanha has ever occurred; but there have been a few cases of poisoning by emetine. The fatal dose and period are uncertain. The symptoms are those of gastro-intestinal irritation and ultimately heart failure. Since the cases of poisoning have occurred mainly in persons undergoing treatment for amoebic dysentery, treatment of the poisoning consists of

withdrawal of the drug and the promotion of its rapid elimination. At necropsy signs of gastro-intestinal irritation are found.

(8)—Morphine and Opium

1513.] The alkaloid morphine combined with meconic acid occurs together with some twenty-five other alkaloids in similar combination in opium. Raw opium is required by the British Pharmacopoeia to contain not less than 9·5 per cent of anhydrous morphine, and the powdered dry opium of the British Pharmacopoeia must contain 9·5 to 10·5 per cent of anhydrous morphine. The salts of morphine in common use are the hydrochloride, sulphate, tartrate, and acetate.

Opium and morphine are subject to the provisions of the Poisons Rules and the Dangerous Drugs Acts, and, although certain preparations of these drugs are exempt from the Dangerous Drugs Regulations, all preparations of morphine fall within the compass of the Poisons Rules (see Vol. X, p. 7). From the toxicological aspect morphine and opium may be considered together with diamorphine (heroin), dilaudid, and other synthetic derivatives of morphine.

In persons unaccustomed to morphine 1 grain of the hydrochloride has on several occasions caused death, and 4 to 5 grains of opium have also been fatal. There are records of death from preparations of opium, the morphine content of which has been less than the fatal quantities indicated above, but their authenticity may be regarded as doubtful. As a general rule, however, the average fatal dose in persons unaccustomed to the drug may be regarded as at least double the figures given above. *Fatal dose*

The human body becomes rapidly habituated to opium; consequently, even although the drug has only been taken for a short time, very much larger doses would be required to produce a fatal result. Thus in one case, a woman dying of cancer required 80 grains of morphine a day to eliminate pain. Children are particularly susceptible to opium and morphine, and very small amounts have been fatal. *Tolerance*

In most cases of fatal poisoning, death generally occurs in 6 to 12 hours, the commonest time being 9 to 10 hours. The quantity taken appears to influence but little the length of the interval between the dose and death. If the patient survives 18 to 24 hours, the chances of recovery are increased. *Fatal period*

There is nothing very striking about the morbid anatomical findings at necropsy. Death takes place in coma with respiratory failure. There is marked cyanosis of the head and extremities. The blood is usually dark and fluid. The viscera are congested, slightly oedematous, and cloudy. The congestion may be especially noticeable in the brain and lungs. The stomach contents may have the characteristic smell of opium, but this will be absent in poisoning by morphine. In death the pupils are not contracted and may be dilated. *Morbid anatomy*

If a poisonous dose is taken by mouth, the symptoms generally begin in 10 to 30 minutes, according to the state of the stomach. If the dose *Symptoms*

is administered hypodermically, the symptoms appear more rapidly. Severe symptoms of poisoning and even death may occur after rectal administration, and severe poisoning when the drug has been incorporated in poultices applied over broken skin. At first there may be some slight mental exhilaration combined with a quickening and strengthening of the pulse. This is said to be more apparent with opium, due no doubt to the associated alkaloids. There may be nausea and occasionally vomiting. Soon follow dizziness, heaviness of the head, languor and drowsiness, and a desire to sleep. This desire is irresistible, and sleep soon comes on. The pulse at this stage becomes slow and weak. The patient has a pleasing euphoria with rapidly changing and pleasant series of ideas. At this stage the patient may be awakened by shouting or by physical stimulation. There is a gradual loss of muscular power and diminished sensation. The sleep passes into coma, pupils are pin-point, and conjunctival reaction lessens and is finally abolished. The pulse is slow and feeble, and respiration is slow and shallow and towards the end periods of a quarter to half a minute may elapse without any respiratory action. When respiration re-starts it is often of the Cheyne-Stokes type. The face is bluish, the extremities are livid, the skin is moist and clammy and, although the body may feel warm to the touch, the temperature is subnormal.

Death is ushered in with cessation of respiration, the heart perhaps beating for a time after the respiration has ceased. In the terminal stage, when the patient is quite flaccid and the end is near, the pupils often dilate, so that a patient seen for the first time at this stage may lead the practitioner to think that the case is not one of morphine poisoning.

Treatment

The stomach should be washed out immediately with a dilute solution of potassium permanganate, but, since potassium permanganate is a powerful oxidizing agent and decomposes morphine, it is desirable that the first stomach contents removed should be free from this substance if an analysis of the poison is required, which is especially important when the nature of the poison is not known. Since morphine is excreted into the stomach, gastric lavage is advised even when the morphine has been administered hypodermically. The lavage should be repeated again in four hours and a third time if the patient's condition warrants it. High colonic lavage should also be practised two or three times at about four-hour intervals.

If the patient is still in the drowsy or in the pre-comatose stage, mechanical and electrical stimulation may be used to prevent or delay coma, but it is doubtful if it is justifiable to walk the patient about and flagellate him. Stimulants, especially respiratory stimulants, should be administered. A warning is necessary about atropine, which, although it may be given generously, should not be pushed so far as to produce poisoning in persons not under the influence of morphine.

Oxygen and carbon dioxide are required in the later stages, and, when signs of failing respiration are observed, artificial respiration should be persevered with until the end; a respiration chamber should be used if

possible. The bladder should be watched and if necessary catheterized, all the urine drawn off being reserved for analysis if required.

For chronic poisoning see title DRUG ADDICTION, Vol. IV, p. 247.

Chronic poisoning

(9)—Nicotine

1514.] This alkaloid occurs in tobacco, *Nicotiana tabacum*, and is the only alkaloid of importance in the plant. In the pure state it is a liquid, and it is the only alkaloid, apart from coniine, of toxicological significance which is not solid at ordinary temperatures. It forms salts, such as the sulphate, all of which are solids. The pure alkaloid is a pale-yellowish oil, but ordinary commercial samples are dark-brown owing to changes produced by the action of light.

Physical properties

Cases of poisoning are met with occasionally not from smoking but in connexion with the use of this alkaloid in horticulture as an insecticide; accidental poisoning may thus be due to sprays used or be suicidal from the drinking of the nicotine preparation. Central scotoma in heavy smokers is stated to be due to nicotine.

The prevalence of tobacco smoking, with the resulting tolerance from the small quantities of nicotine absorbed, makes it difficult to fix a possibly fatal dose. Further, the commercial preparations of the alkaloid vary much in composition. Probably a few drops of the pure liquid alkaloid would prove fatal in most instances. When considerable doses have been taken, death occurs in a few minutes. Next to hydrocyanic acid, nicotine is the most rapidly acting poison known.

Fatal dose

Fatal period

The facial expression may be staring and the pupils dilated. The smell of tobacco may be present in the gastric contents, in the upper food-passages, and sometimes also in other viscera. If death has not been immediate, there may be inflammatory changes on the exposed mucous surfaces. Death is apnoeic, there is venous congestion of the viscera, and the blood is dark and fluid.

Morbid anatomy

Large doses of the alkaloid produce a hot burning sensation in the mouth, spreading down the oesophagus to the stomach. Salivation and vomiting generally occur, followed, if the patient survives long enough, by diarrhoea. Mental confusion, muscular weakness, giddiness, and restlessness are often followed by muscular twitching, clonic convulsions, and tetanic spasms. Unconsciousness ushers in death. The pulse is rapid at first, but later it is often slow and feeble. Respiration becomes slow and weak and finally stops, the heart continuing to beat after respiration has ceased. Thus nicotine is essentially a respiratory poison. Very large doses may prove fatal in an extremely short time from paralysis of the central nervous system and abolition of respiration.

Symptoms

When large doses have been taken, the rapidity of death prevents any effective treatment. Gastric lavage with tannic acid solution is the best treatment and should be followed by general eliminative measures if the patient survives. Stimulants, particularly those acting on the respiratory centre, warmth, and oxygen with carbon dioxide should be tried.

Treatment

(10)—Physostigmine

1515.] *Physostigma venenosum* contains the alkaloid physostigmine (eserine). Very little is known about the toxic effects of this drug, and no opinion can be expressed concerning the fatal dose and period. The symptoms due to a poisonous dose taken by the mouth appear to be continuous vomiting, salivation, epigastric pain, and contraction of the pupil.

The treatment consists in the removal of the poison and of the treatment of such symptoms as may occur. No characteristic sign is found at necropsy.

(11)—Strychnine and Brucine*Source*

1516.] Various species of the genus *Strychnos* contain the alkaloids strychnine and brucine; *Strychnos nux vomica* and *Strychnos ignatii* are the most important, and of these only the former is official. The plant does not grow in Great Britain. The beans of *nux vomica*, the part of the plant which is official, contain 1·8 to 5·3 per cent of total alkaloids, of which about one-half is strychnine. The St. Ignatius bean contains 2·5 to 3 per cent, of which rather more than one-half is strychnine. The B.P. preparations of the bean are all standardized in terms of their strychnine content. The pure alkaloid strychnine is official as the hydrochloride, but brucine is not official.

Owing to the terrible effects of a poisonous dose in both man and animals, sale of the alkaloid and its preparations except to laboratories, to medical men, and in compounded medicines is now prohibited. Consequently the sale of strychnine vermin-killers is not now allowed.

Strychnine

The alkaloid strychnine in the pure state occurs as prismatic needle-shaped crystals and on account of this has been mistaken for certain non-poisonous inorganic salts, e.g. magnesium sulphate. It is an intensely bitter substance, the taste being appreciable even in a 1 in 600,000 solution in water.

Fatal dose

Half a grain has proved fatal on more than one occasion and must therefore be regarded as a possibly fatal dose; but recovery has followed after much larger quantities.

Fatal period

Death generally supervenes in 1 to 3 hours, but it has occurred much more rapidly. After three hours the chance of recovery increases the longer the patient lives.

Morbid anatomy

The heart is dilated, and the lungs are slightly oedematous. The blood tends to be fluid and the organs to be congested and dark. There are petechial haemorrhages on the skin, pleurae, and mucous surfaces. Sometimes the capillary haemorrhage is ecchymotic. In cases predisposed by vascular disease there may be cerebral haemorrhage. The muscles may show microscopic evidence of tearing, and the associated haemorrhage may be visible to the naked eye. There may be marks of superficial bruising due to injury.

The symptoms generally begin in 10 to 15 minutes after a possibly fatal dose has been taken. The patient at once notices a bitter taste, and, although the food or drink is therefore rejected, some of it is generally swallowed, with the result that the symptoms occur. This explains its successful use in homicidal cases in spite of its bitter taste.

The first symptoms are either stiffness of the muscles of the neck and a tightness in the chest, which on account of respiratory uneasiness renders the patient anxious, or stiffness of the lower extremities. Soon stiffness spreads to other muscles, and the patient's movements become jerky, so that an attempt to pick up an article results in it being knocked over. The anxiety increases, together with a feeling that something terrible is going to happen. In about half an hour the patient experiences a sudden and severe convulsion. All the voluntary muscles are violently and painfully contracted, the greater power of the extensors producing full extension with feet arched and arms extended or drawn across the chest; extension may be so excessive that the body becomes arched, resting only on the occiput and the heels—opisthotonos. The contractions are tonic, but there may be momentary relaxations, with the result that during a part of the convulsions they may appear to be clonic.

During all this time the patient is fully conscious and suffers the most acute mental and physical pain. He becomes cyanosed from the fixed contraction of the muscles of respiration, and his pulse is rapid and feeble. The fits at first are short, less than half a minute, and followed by a period of relaxation varying from a quarter of a minute to several minutes, during which the patient can breathe and the heart's action improves, but he lies exhausted, bathed in sweat, with the surface of his body cold and his pupils contracted, and he suffers mental agony and dread of what is to come.

After a time a second fit occurs and then a third and so on, each succeeding fit being longer, more violent, and followed by a shorter period of relaxation, until one of three things may happen: (i) the patient may recover; in this event the severity of the fits gradually diminishes, and the intervals are longer, until fits pass off, and the patient, except for exhaustion, will then make a rapid recovery; (ii) he may die of asphyxia during a fit; or (iii) he may die of heart failure either during or between a fit. In either event his mind is clear, and he is conscious to the end.

In the period of relaxation the least stimulus, e.g. touching the patient or the bed, flashing a light, and banging a door, will start another fit. The patient is thirsty but dare not drink for fear of a fit.

Strychnine poisoning may resemble tetanus when the patient is at the height of an attack, but the history of the case, the rapidity of onset of symptoms, and the complete relaxation between the spasms in strychnine poisoning should clearly differentiate the two conditions. Tetanus is characterized by the risus sardonicus, and the disease lasts days not hours. Strychnine poisoning has been mistaken for status epilepticus, but the consciousness of the patient in all stages rules out epilepsy.

Treatment

If the patient is first seen before the onset of the convulsions, the stomach should be washed out at once with a solution of tannic acid. Failing tannic acid, a very weak solution of iodine or a suspension of adsorbent charcoal may be used. When this has been done, a full dose of chloral hydrate should be left in the stomach. The patient should be placed in bed in a darkened room under the quietest conditions and never left. Chloroform and ether should be at hand with the necessary means of administration, so that the patient may be anaesthetized as soon as there is the slightest sign of the onset of convulsions. As soon as he is under, the anaesthesia should be kept as light as possible but sufficient to control the fits. Physiological saline may with advantage be given intravenously or subcutaneously to hasten the elimination of the drug, and a catheter should be passed, if necessary. The colon may be washed out during this period and if necessary another dose of chloral hydrate given.

As soon as there is evidence that the convulsions are ceasing, the anaesthetic may be gradually withdrawn. It will probably be advisable to wash out the stomach a second time 3 to 4 hours after the first washing. If the patient is seen for the first time during convulsions, he should be anaesthetized at once, so that the convulsions may be controlled and the patient relieved from agony. When the convulsions are controlled, gastric lavage and the other measures described above can be proceeded with. It will probably be desirable to continue the chloral hydrate for a few days during convalescence.

Brucine

This alkaloid, except in the laboratory, is only met with mixed with strychnine, i.e. in preparations of *nux vomica*. It resembles strychnine in its action but is very weak and only slightly toxic. Probably 20 to 25 grains would be necessary to cause death, and it is doubtful if any authenticated cases of poisoning by this alkaloid alone have occurred.

*Diagnosis
from
strychnine
poisoning*

From an analytical standpoint cases of poisoning by *nux vomica* preparations may be distinguished from cases of poisoning by strychnine by the presence or absence of brucine in the viscera. Such investigations may be helpful in tracking down the source of the poison.

(12)—Veratrum

1517.] The *Veratrum* genus of plants contains several poisonous alkaloids, the toxic properties of which may be considered together. No opinion can be expressed about fatal dose or period. The symptoms are burning and pricking of the mouth, epigastric pain, salivation, thirst, nausea, and vomiting. Violent purging with colic and tenesmus follow. The prickly sensation spreads over the body, and the skin is often erythematous. The pupils are dilated. Death is due to respiratory failure. Treatment consists of gastric lavage and the administration of opium or morphine and respiratory stimulants. Evidence of gastro-intestinal irritation is found at necropsy.

6.—CANTHARIDES

1518.] Cantharidin is the lactone of a complicated organic acid which occurs in the bodies of cantharides (Spanish fly, *Cantharis vesicatoria*) and allied species. When applied to the skin it sets up local inflammation with the formation of small blisters, which soon coalesce into a single large blister. From time immemorial it has been a reputed aphrodisiac, but its effects in this direction are grossly overrated; it and also yohimbine are alleged to be ingredients of aphrodisiacs sold to wealthy Eastern potentates. Cantharides is recommended as an ingredient in hair restorers, and it is stated to be a constituent of some preparations supplied to cattle and horse breeders.

It is not possible to fix the fatal dose, but 25 grains of the powdered beetle is stated to have caused death, and according to Leschke about 0.5 grain of cantharidin may be considered as an average fatal dose.

The fatal period varies.

Fatal period

The mucous membrane of the intestinal tract is acutely inflamed with ulceration and vesication in places. The kidneys show a parenchymatous inflammation, and the bladder and urethra may be inflamed.

Morbid anatomy

The action of cantharides is essentially an intense local irritation. Taken by the mouth it causes pain in the mouth and stomach, intense thirst, vomiting, and purging. The vomit and the stools will contain blood. Pain in the loins and lower abdomen, with strangury and the passage of urine containing blood, are common. Priapism in the male and abortion in the female have been recorded. Headache, delirium, convulsions, coma, and collapse may lead to a fatal termination. If the acute symptoms pass off, the sufferer may be left with nephritis which may prove fatal.

Symptoms

The stomach must be washed out as soon as possible. Albumen water and demulcents may be given, but oily substances must be avoided. Morphine will probably be necessary to relieve the pain.

Treatment

7.—INORGANIC AND METALLIC

(1)—Antimony

1519.] Poisoning by antimony is not common now. Apart from the use of compounds of antimony in the treatment of certain tropical diseases, its use in general medicine has almost disappeared. In industry the metal is alloyed for various purposes, e.g. type metal, the oxide in enamelling, the sulphide in vulcanizing rubber; certain compounds are employed as mordants in fire-works; and the trichloride (butter of antimony) is used in the furniture trade and by gunsmiths. The use of the oxide as a glaze in enamel ware has been responsible for cases of poisoning when certain types of enamel vessels have been used to prepare acid beverages, e.g. lemonade. Occasionally the chloride (butter

of antimony) has been taken with suicidal intent. The chloride (SbCl_3) in contact with water decomposes into antimony oxychloride (SbOCl) and hydrochloric acid; these cases should therefore be regarded as cases of poisoning by hydrochloric acid and antimony (see p. 70). In most cases of homicidal poisoning with antimony the poison administered has been tartar emetic (potassium antimonyltartrate).

(a) *Acute Poisoning*

Fatal dose It is very difficult to fix a fatal dose of this poison, because a very early and characteristic symptom is vomiting. A dose of 2 grains of tartar emetic is recorded as having caused death in an adult, but probably doses of about 10 grains must be regarded as a quantity likely to kill. Recovery has followed ingestion of more than 150 grains.

Fatal period The fatal period varies much; patients have lived from a few hours to several days.

Morbid anatomy The post-mortem appearances closely resemble those in arsenical poisoning. The intestinal tract is red, the mucosa is swollen, and there are submucous haemorrhages and ulceration. The contents may consist largely of blood-stained mucus. The organs show signs of parenchymatous degeneration. If the patient has survived long enough or has received more than one dose, fatty changes will be observed in the liver, kidneys, and heart-muscle. As in poisoning by arsenic, the body is as a rule well preserved.

Symptoms An acrid metallic taste (except in poisoning by antimony trichloride), with a sense of constriction and pain in the throat and pain in the stomach, is followed in 15 to 30 minutes by frequent and profuse vomiting. Later there is diarrhoea, with watery stools and tenesmus. The pulse is at first accelerated, but the arterial blood-pressure soon falls, and the pulse becomes slow and irregular. Perspiration and salivation are profuse, the skin is cold and clammy, and there is generally cyanosis of the face and extremities. Cramps in the calves may be followed by generalized spasmodic contraction. Attacks of vertigo and syncope occur until consciousness is lost, and death results from heart failure. The urine is scanty and may be suppressed; it often contains albumin.

In poisoning by antimony trichloride the patient will also show signs of hydrochloric acid poisoning (see p. 70).

Treatment The treatment described under arsenical poisoning (see p. 111) may be applied for this poison, except that the liquid used to wash out the stomach should contain tannic acid and not ferric hydroxide. If antimony trichloride has been taken, the stomach pump should not be used, because the hydrochloric acid liberated has exerted a destructive action on the walls of the stomach, and alkalis other than carbonates must be given, in order to avoid distension of the stomach by gas.

(b) *Chronic Poisoning*

In industry chronic poisoning by antimony is practically unknown, but when the poison has been used homicidally and when a series of

doses has been given, sickness, abdominal pain, loss of appetite, diarrhoea, and prostration, with sweating and feeble pulse, have been recorded.

(2)—Arsenic

1520.] The importance of arsenic as a poison cannot be over-estimated. It has been in use for centuries as a favourite homicidal poison, and in Eastern countries there are hundreds of cases every year. Besides the ease with which it may be administered, owing to the small amount required and to the tastelessness of many of the compounds, its wide-spread use for a number of purposes renders it easily accessible to the public. No doubt in the East the use of this substance as a depilatory in the harem provides a convenient source of supply.

The fact that many cases of homicidal poisoning in this country have only been discovered after an exhumation further emphasizes the importance of the poison and demonstrates how easy it is to mistake the symptoms of poisoning for natural disease, such as food poisoning.

On the other hand, from the analytical standpoint this poison can perhaps be more easily detected than any other poison and the amount present determined with the greatest accuracy, even when the minutest trace only of the poison is present in the body; and in cases of chronic poisoning analytical investigation of the epidermal structures may reveal conclusive evidence of arsenic. *Detection by analysis*

In view of the toxic nature of this poison and the ease with which it can be excluded from food and drink the Royal Commission in 1903 laid down that the maximal quantity to be permitted in food was $\frac{1}{100}$ grain per pound and in drink $\frac{1}{100}$ grain per gallon. This standard is generally accepted.

Compounds of the metalloid arsenic are very widely distributed in nature. They occur in various concentrations in a number of ores, in coal, and in the soil of certain localities. Some edible fish, crustacea, and molluscs contain appreciable traces of arsenic. *Natural distribution*

The following compounds of arsenic are used for various purposes, and most of them are available to the public: sodium and potassium arsenite, sold as such and in arsenical sheep-dips, weed-killers, cattle-dips, hide preservers, worm powders and tablets for animals, fly powders for external application to sheep, preparations for foot-rot of sheep, and preservative solutions for wood; arsenious oxide in arsenical sheep-dips, powder for destruction of ants, and fly powders for external application to sheep; sodium arsenate in arsenical sheep-dips and fly powders for external application to sheep; arsenic sulphides and thio-arsenates in arsenical sheep-dips and fly powders for external application to sheep; arsenic acid in arsenical weed-killers; copper arsenite and arsenate in arsenical worm powders for animals; lead arsenate—either PbHAsO_4 or $\text{Pb}_3(\text{AsO}_4)_2$ —in horticultural spray or dust; calcium arsenate, magnesium arsenate, manganese arsenate, and zinc arsenite in horticultural spray or dust; London purple—calcium arsenite and *Industrial uses*

calcium arsenate—in horticultural spray or dust; and Paris green—copper aceto-arsenite—in horticultural spray. Arsenical soaps also are probably in fairly general use, and certain arsenical compounds are used as ingredients in anti-fouling paints for ships' bottoms. With the possible exception of soaps and anti-fouling composition all the above-mentioned compounds can produce fatal poisoning if taken by man.

Arseniuretted hydrogen is a gas which from time to time gives rise to poisoning in industry (see p. 162).

Fatal dose

It is well established that a dose of 2 grains of the poisons expressed as arsenious oxide has caused death. This figure is given on the understanding that the form in which the arsenic is taken can be dissolved in water or in the body fluids. No doubt a greater quantity of the less soluble or the insoluble forms would be required. Recovery often occurs after doses of 2 grains, and the average fatal quantity is 4 grains and upwards. Early and persistent vomiting makes it impossible to form any opinion, apart from analysis, about the quantity of poison absorbed. Thus, recovery has occurred after several hundred grains have been swallowed.

Fatal period

The average fatal period of a case of arsenical poisoning is about thirty hours, but some cases have proved fatal in two hours, and others have been prolonged for several days. Symptoms generally appear in one-half to one hour, but they have been known to occur almost at once and to have been delayed for several hours. Generally speaking, the earlier the symptoms the more severe the case and the greater the probability of a fatal end. These remarks apply to the poison taken by mouth, but cases of poisoning, some of which have proved fatal, have occurred when the poison has been given *per rectum* in an enema and *per vaginam* to procure an abortion.

Morbid anatomy

The post-mortem appearances depend on dosage, mode of entry, and time of survival. When a poisonous dose of arsenic has been taken by the mouth, the most striking changes are seen in the upper part of the alimentary tract, more particularly in the stomach. When the poisoning has been by another route, e.g. from a skin plaster contaminated with arsenic, the most intense changes occur at the site of entry, but some inflammation of the stomach is seen also in these cases. When there have been previous sublethal attacks, the changes, e.g. in the skin, conjunctivae, and peripheral nerves, of chronic arsenical poisoning may be superadded to the acute. If, on the other hand, death from exhaustion has followed the single or final dose after a period of several weeks, the inflammatory changes will have subsided, and the poison, except for possible traces in keratin, may have been completely eliminated.

The post-mortem findings of acute arsenical poisoning by the mouth are as follows. The mucosa of the mouth, pharynx, and oesophagus is inflamed, but the effects here are usually slight. In a case in which the oesophageal mucosa was reddened microscopical examination showed dilated venules and capillaries, some oedema, and emigration of polymorphonuclear leucocytes.

The changes are most pronounced in the stomach, which, owing to the vomiting, is usually emptied of all food residues and contains a mucoid fluid tinged with blood and bile, with flakes of mucus in suspension. The mucosa is inflamed, slightly swollen, and in places coated with mucus. The colour varies with the severity of the case from a dull brownish red to bright scarlet. Even when the whole gastric lining is affected, the changes are more marked in the fundus, especially along the longitudinal folds, which often show petechial haemorrhages and erosions. Sometimes masses of pasty white arsenic may be found adherent at points where the underlying mucosa is severely damaged, haemorrhagic, and black. Perforation has been recorded, but is extremely rare. *Stomach*

The inflammation extends into the small intestine throughout, the affected mucosa being smooth, swollen, and reddish-brown. The contents may be mucoid and blood-stained, as in the stomach. The large intestine may be empty of its normal contents and contain rather more mucus than normal, and may be reddened. The rectum is usually inflamed. *Intestine*

The viscera are congested and show parenchymatous degeneration. In the liver and kidneys there is some fatty change. The endocardial surface of the left ventricle often shows petechial haemorrhages. From the extreme dehydration the skin becomes loose and the eyes sunken. The blood is concentrated from the loss of fluid, the polycythaemia partly accounting for the cyanosis seen before and after death.

There is little doubt that arsenic when present in large amount delays post-mortem putrefaction. Signs of gastric inflammation have been discerned even after burial for many months. It is probable, however, that the preservation—post-mortem ‘mummification’—noted in many cases of arsenical poisoning is partly due to the dehydration of the tissues during life.

(a) *Acute Poisoning*

Witthaus divided the symptoms of arsenical poisoning into two types: *Symptoms* (i) gastro-intestinal, which is the commonest, and (ii) narcotic. When a poisonous dose of an arsenical substance is taken, no appreciable taste is noticed in most cases, and, when it is administered in solid form in food, no taste of arsenic will be noticed.

Gastro-intestinal form

The first symptoms are irritation and heat in the throat, soon followed by faintness, depression, and nausea. Vomiting and retching soon follow; the vomit is at first chiefly food, but later it is almost entirely mucus, often tinged with blood; when the arsenical preparation taken is coloured or contains colouring matter, this may be noticed. Abdominal pain soon follows first in the epigastric region but without delay radiating out over the abdomen. The pain is burning and has been described as like a red-hot coal on the stomach. The abdomen is very tender, and the pain is increased by touch or palpation. The tongue is covered with

white fur, the mouth is dry, and there is a sense of constriction in the throat. The retching continues, and any attempt to allay thirst by drinking fluid immediately brings on retching, so that the sufferer soon learns to avoid liquid by the mouth. Diarrhoea occurs later, often after 12 to 18 hours, but the time of its appearance varies. The stools are voided precipitately. The first stool is generally very copious, most of the intestinal contents being voided at one time, and it is accompanied by pain and tenesmus. Other motions follow at short intervals, these being 'cholera-like', consisting of watery material containing mucus and blood. The anus becomes very sore. About the time of the diarrhoea muscular cramps, particularly in the calves, are distressing and painful. The patient is fully conscious, restless, and collapsed. The pulse is small, rapid, and irregular. The skin is cold, clammy, and bluish. The urine, which may contain albumin and casts, is scanty and may even be suppressed. The collapse may soon usher in death, and the patient, although usually conscious to the last, may have convulsions and lose consciousness at the end.

Since the condition is sometimes mistaken for food poisoning, it may be worthy of note that in food poisoning retching and vomiting do not persist, and vomiting may only occur once. Further, the time between the taking of food and the onset of symptoms is often several hours, whereas it is not as a rule more than about one hour in arsenical poisoning. The diarrhoea comes on earlier in food poisoning, and in most cases the abdominal pain, tenderness, and cramp are much less severe.

Narcotic form

The gastro-intestinal symptoms are not severe and may be absent. The patient becomes sleepy and unconscious, sometimes with delirium, and dies without regaining consciousness. The duration of the illness is shorter, lasting as a rule 4 to 8 hours. It is a very fatal form.

(b) Subacute Poisoning

There is a form of arsenical poisoning in which the patient appears after a short acute attack to exhibit symptoms which are associated with the chronic states. It is sometimes described as subacute poisoning.

The onset is of the violent gastro-intestinal type, and in 24 to 48 hours the symptoms pass off. The abdomen may remain tender, with soreness of the mouth and throat, swelling of the salivary glands, severe and persistent thirst, and no desire for food. Temperature is high. The urine is diminished and contains albumin and casts. Often skin rashes appear which may take almost any form. Headache, restlessness, and sleeplessness are troublesome. The eyes are suffused and the conjunctivae injected, and the nasal mucosa is inflamed. The strength fails, the limbs are weak or paralysed, and the heart is rapid, feeble, and irregular. The patient's mind wanders, consciousness is often lost towards the end, and convulsions may usher in death. Jaundice some-

times occurs. Death in this type may occur in 5 to 10 days. When the possibility of homicidal poisoning is under consideration, it must be remembered that the poisoner may at any stage of the illness give a second or third dose, especially if the sufferer appears to show signs of recovery. Thus the symptoms associated with the early stage of an acute attack may be superimposed upon the clinical picture of a later stage; it may then be difficult to establish clinically the true diagnosis. The diagnosis can only be confirmed by chemical analysis, and for this purpose the first samples of vomit, faeces, and urine are the most important to preserve, because they contain the greatest quantity of the poison.

The stomach should be washed out with copious quantities of water, to which may be added some freshly prepared ferric hydroxide, made by precipitating it from ferric chloride with dilute ammonia solution. The precipitate should be squeezed out in muslin and washed to remove excess of ammonia. At the conclusion of the washing a quantity of the ferric hydroxide should be left in the stomach. The gastric lavage should be repeated at intervals until the acute symptoms begin to subside. Owing to the loss of fluid from the vomiting and diarrhoea, saline must be administered intravenously or subcutaneously according to the patient's condition to make good the loss and to assist in elimination of the poison by the kidneys. Since arsenic is a powerful liver poison, it may be desirable to add some glucose to the saline. Morphine will be required for the pain, and the condition of the heart must be carefully watched and stimulants given as required. *Treatment*

(c) *Chronic Poisoning*

This may follow an acute attack; the first signs do not usually appear until at least twelve days have elapsed from the original dose. It may also arise from the continued taking of arsenic over a period of time.

The symptoms may be conveniently grouped as follows:

Symptoms

(i) *Digestive disturbances.* The case often starts with symptoms which to some extent suggest a mild form of an acute attack. There are vomiting and abdominal pain with constipation perhaps alternating with diarrhoea. The gums are inflamed, and the tongue has a white silvery coating. Febrile symptoms with a rapid pulse may be observed. These symptoms last but a short time and may be absent.

(ii) *Catarrhal disturbances.* These symptoms may be associated with the secretion of arsenic into the mucous membrane lining the air-passages. There is laryngeal and bronchial catarrh with a dry cough and a hoarse and husky voice; the fauces are congested and the vocal cords thickened. At the same time there are marked coryza, congestion of the conjunctivae, and watering of the eyes. The patient often complains that he can only read for a short time.

(iii) *Cutaneous disturbances.* About this time various skin lesions may appear; they are more commonly seen when small doses of the poison have been taken over a long period. Various erythemas, herpes, and

pigmentation may occur; a grey or greyish-brown pigmentation can occur on face, neck, loins, abdomen, and genitals. Keratosis is also commonly seen on the palms of the hands and on the soles of the feet, but it may occur generally, making the skin thick, rough, and coarse. Thickening and loss of the nails may occur, and warts have been described.

In the arsenic industry workers who have been long exposed to arsenical dusts may develop epitheliomatous ulceration of the skin and perforation of the septum of the nose (see p. 137).

(iv) *Neuritic disturbances*. At first there is a feeling of numbness in the legs, with tingling, burning, and pricking sensations, and the patient complains that he feels as if he were walking on cotton-wool. These sensations may soon spread to the hands. Later there are severe, often shooting, pains, and the muscles of the legs and arms are tender on pressure. There is some diminution of sensation; light touch may not be perceived, and a pin must be very firmly pressed against the skin for it to be appreciated. The special senses generally escape, but there may be loss of sexual desire.

(v) *Motor disturbances* generally follow, rapid fatigue being the first complaint. The paralysis may increase with the characteristic gait, and soon the patient becomes bedridden. Reflexes may be increased at first but later are lost. Wasting is pronounced. In very severe cases the paralysis may extend to the abdominal muscles. In the upper limbs the small muscles are the first to be affected, but in severe cases the arms may be affected. Associated with these symptoms is damage to the heart muscle, leading to heart failure, exhaustion, and anaemia.

In most cases recovery occurs but is slow and may take a year. Death is generally due to syncope. The treatment is elimination of the poison and the application of suitable massage and electrical treatment to the affected muscles.

(3)—Barium

1521.] Compounds of this metal, the nature of which are unknown, are found in the kernels of Brazil nuts in amounts varying from 0.02 to 0.3 per cent.

Salts of this metal may be classed into (i) those soluble in water, e.g. the chloride, all of which are irritant poisons; (ii) those soluble in the body fluids, e.g. the carbonate, which is also an irritant poison; and (iii) those insoluble, e.g. the sulphate, which is harmless and is used in radiography. Fatal cases of poison, however, have been recorded from the use of the carbonate in mistake for the sulphate, both these salts being white powders.

Barium salts have many uses, the carbonate being used as a rat poison, the sulphide as a depilatory, the nitrate in fireworks to produce a green flame, the chlorate in dye works, and the chromate as a pigment.

From 70 to 100 grains may be regarded as a possibly fatal dose but, as with all irritant poisons, the early and copious vomiting explains

why much larger quantities have not proved fatal. The fatal period *Fatal period* varies.

In the upper food-passages at necropsy there are inflammatory changes with the typical distribution of an irritant poison, i.e. in the pharynx, lower end of the oesophagus, and especially in the stomach, where they are most pronounced in the fundus, on the posterior wall, and along the rugae. Where most affected the gastric mucosa may be haemorrhagic, but ulceration is uncommon. There may be excess of mucus on the surface, and some of the poison may be found, but the organ is generally emptied of all food residues. The purging is associated with inflammation of the rectum. The viscera are congested and show parenchymatous degeneration. *Morbid anatomy*

Acting locally as an irritant, it produces violent pains in the stomach and abdomen with nausea, retching, and vomiting, followed later by purging; blood may be found in the excreta. After absorption barium salts act specifically on muscular tissue, causing vigorous muscular contraction; its action on the myocardium is said to resemble that of digitalis. The heart-beat is increased in force and frequency, blood-pressure rises, and in fatal cases the heart is stopped in systole. The poison also acts on the central nervous system, eventually producing coma with convulsions and in some cases paralysis. *Symptoms*

Barium is one of the few poisons for which there is a perfect antidote, i.e. soluble sulphates, e.g. magnesium and sodium sulphates. The stomach should be washed out with a solution of one of these salts and a considerable quantity of the salt left in the stomach. *Treatment Antidote*

Morphine and the general treatment of shock will be necessary, and the condition of the heart, in view of the specific action of barium on this organ, requires careful watching. Should the vomiting and diarrhoea have been excessive, subcutaneous saline to replace fluid will be indicated.

(4)—Lead

See LEAD POISONING, Vol. VII, p. 658.

(5)—Mercury

1522.] Numerous salts of this metal are used in medicine for various purposes and increasingly in horticulture as insecticides and seed dressings, in the paint and varnish industry, in fur dressing, and in wood preserving, and the metal itself in many scientific instruments. *Industrial uses*

The metal is a poison. It has produced fatal results after being taken by the mouth and after inunction, but perhaps most dangerous of all is the breathing of fumes of heated mercury. The globules, being very finely divided, are rapidly absorbed and produce serious illness. The salts of mercury vary considerably in their solubility in water, but every salt of mercury, except perhaps mercurous chloride (calomel), must be regarded as a potential poison owing to chemical change that may take place in the intestines. *The metal Salts*

(a) Acute Poisoning

Fatal dose Although fatal results have been recorded with almost every salt of mercury, it is expedient here to give only one or two examples of fatal doses. Roughly speaking, the less soluble the salt in water the greater the amount necessary to cause death. Thus death has resulted from 5 grains of mercuric chloride and of the basic sulphate, whereas a dose of 35 grains of ammoniated mercury has been recorded as fatal.

Fatal period Death may occur in the acute stage, i.e. within the first day or two, or may occur at a later stage, generally in the second week, from the effects of the poison on the kidneys.

Morbid anatomy The post-mortem appearances in a case of poisoning by mercuric chloride vary with the mode of administration and the time of survival. When the poison has been taken by the mouth and death has ensued early, the tongue and lips are swollen and the mucosa of the mouth is coagulated and white. Similar changes are found in the pharynx and oesophagus. In places, e.g. the fauces and the lower end of the oesophagus, the necrosed surface may be broken up and shreddy. In some cases there may be great oedema of the loose tissues of the valleculae and the laryngeal vestibule which may be fatal from asphyxia. The gastric mucosa is corrugated and may show inflammatory or petechial reddening. This is obscured, however, by the fixation necrosis of the surface, so that the colour is usually a greyish violet. Exceptionally a black haemorrhagic condition has been described. Perforation is very uncommon but may result from the continued contact in one place of the poison in solid form. Similar changes may extend for a short distance into the duodenum, and all cases will show inflammatory changes throughout the small intestine.

When survival has been longer, the initial corrosive effects have generally been less intense. In the stomach they may actually be healing, but in the mouth, especially on the gums, they have generally gone on to ulceration. Septic lymphangitis and parotitis may be present.

Intestinal changes The large intestine usually shows characteristic changes which resemble bacillary dysentery. In rapidly fatal cases there may be only some acute inflammation. Quickly, however, this is increased, and diphtheroid necroses appear and ulcerate. In the origin and distribution of these lesions infective and mechanical factors appear to play a part. They often occur on the crests of the transverse folds or in relation to the longitudinal muscular bands. The condition increases towards the rectum and is generally maximal in the sigmoid, where the ulceration may be confluent. In severe cases even the lower ileum may be involved.

In the kidney severe changes are almost invariable. They may be very marked even when death has taken place early, their intensity depending mainly on the amount of poison absorbed. In early cases the organ is swollen and the cortex pale. Tubular degeneration is present and possibly glomerular necrosis and inflammation. The first convoluted tubule and ascending loop of Henle may show various changes from severe cloudy swelling to complete necrosis. Casts are numerous, mainly

granular. In late cases calcification of necrosed epithelial cells and debris may be a conspicuous feature, and the organ may grit on the knife.

When the poison has been introduced by any other route, e.g. intravenous, the pathological changes in the kidneys and colon are similar. The stomach is unaffected. In the mouth, however, ulceration is usually present, its appearance seeming to depend on the previous presence of oral sepsis. When death has followed the introduction of the poison into the vagina, there are local corrosion and sometimes perforation or peritonitis.

The acuteness of the symptoms varies with the salt taken, those *Symptoms* readily soluble producing much more acute effects than those less soluble. One of the commonest mercurial salts met with in poisoning and one which is readily soluble in water is mercuric chloride, which may be taken as a typical salt for purposes of description. An acrid taste is accompanied by a sense of constriction of the throat. A burning *Acute stage* sensation is felt from the mouth to the stomach, followed rapidly by such acute pain over the whole of the abdomen that the patient cries out in agony. Nausea, retching, and vomiting soon occur, the vomit generally containing blood and greyish-white fragments of coagulated mucous membrane from the gullet and stomach. A white coating is noticed in the mouth on the tongue and throat, and inflammation may involve the glottis or the air-passages, hindering respiration. Later there is diarrhoea with watery stools containing fragments of coagulated mucous membrane and blood. From the first the patient is in a state of severe shock, with subnormal temperature, rapid, irregular, and feeble pulse, and a cold clammy skin, and death may occur in the early stages from collapse, with unconsciousness or with convulsions. Death in the acute stage may occur in an hour or two or within the first two days, but if this stage is reached the acute symptoms will generally be recovered from. The urine is generally scanty or suppressed, and any voided will contain albumin, casts, and probably blood. Salivation is often prominent after the first few hours.

If the acute stage is safely survived, various complications may set in *Later stage* and may prove fatal. (i) An acute stomatitis may occur with ulceration, continuing salivation, spongy and bleeding gums, and looseness of the teeth. Gangrene has been recorded. (ii) The urine, which may *Stomatitis* or may not have been scanty in the acute stage, should be carefully measured. As a result of the direct action of the poison on the kidneys *Uraemia* the urinary output may steadily diminish until generally in the second week suppression occurs. The approach of the uraemic state is shown by the blood-urea, which shortly before the suppression of urine occurs may amount to 500 to 600 mgm. per 100 c.c. Unless the kidneys can be made to function again, the condition is fatal in a day or two. (iii) The damage to the intestinal tract with sloughing of mucous membrane *Intestinal ulceration* may leave a condition of ulceration of the intestines, particularly of the large intestine, which will result in an ulcerative colitis. This condition,

associated with pain and the passage of blood and mucus, is not usually fatal but is very intractable, and many months may elapse before a cure is effected.

Treatment

The stomach must be at once washed out with copious quantities of water containing egg-white or milk, preferably the former, and at the conclusion of the process a quantity of the egg-white should be left in the stomach. The process should be repeated after an interval of a few hours and possibly a third time. It is also recommended that sodium phosphite or sodium hypophosphite be employed in doses of about 10 grains every eight hours for two to three days, but we have no experience of the treatment. If an acid salt, such as the acid nitrate, has been taken some alkali other than carbonates or bicarbonates must be given in addition. Morphine will be required for the pain and general treatment for the collapse and shock. As soon as the acute symptoms have subsided, a careful watch must be kept on the renal function. The twenty-four hours' output must be carefully measured so that the possible onset of anuria may be anticipated. The urine should be tested and the urea content of the blood measured frequently so that the renal function may be gauged. In those cases in which the kidneys are seriously damaged one of two pictures may occur. (i) The output of urine continuously decreases with a rise in the blood-urea until the onset of anuria appears imminent. Then the output of urine increases and in the course of a few weeks the kidney function appears to be normal again and it will be conjectural as to what permanent damage, if any, has resulted. (ii) A state of anuria will occur. This calls for energetic and active treatment, and undoubtedly surgical interference is the only likely treatment that will hold out hope of saving life, and then only if it is not left too late. The operation consists of cutting down to, and incising the capsules of, both kidneys. The great difficulty is to decide when this should be done. If left too late the attending shock may prove fatal and if performed too early the physician may feel that perhaps, without interference, the kidneys might have commenced to secrete again. Perhaps the blood-urea values and those for the alkali reserve may assist in this direction. For the rest, the stomatitis and colitis should be treated on general lines appropriate to these conditions.

(b) Chronic Poisoning

See p. 138.

(6)—Phosphorus

1523.] Phosphorus occurs in two forms: yellow and red. Yellow phosphorus is rapidly oxidized in the air and must be kept under water, whereas red phosphorus, which is prepared by heating the yellow variety to 200° C. in the absence of air, is stable. Red phosphorus has no poisonous properties, owing to its insolubility in water and in the body fluids.

Poisoning by yellow phosphorus has become very much less common, *Yellow phosphorus* because the commonest source of the poison, i.e. matches containing yellow phosphorus, is no longer purchasable. Practically the only source of yellow phosphorus available to the public is certain rat poisons, e.g. rodine, which contains the phosphorus in an oily suspension, thus preventing oxidation, so that it will keep for a considerable time. Rat poisons containing phosphorus can usually be recognized immediately by the characteristic odour of the element.

(a) *Acute Poisoning*

It is difficult to estimate the average quantity which should be regarded *Fatal dose* as fatal, because many of the reported cases of fatal poisoning occurred after eating a number of match heads or swallowing a quantity of rat poison. Since the amount of phosphorus in the article concerned is not accurately known, the dose taken cannot be fixed. Further, a fine suspension of phosphorus or a solution in oil is far more active than coarse particles, but much of it may become oxidized to phosphoric acid before absorption. About 2 grains, however, is usually regarded as a lethal dose.

The clinical picture is divided into two periods with an interval of *Fatal period* remission of symptoms. Thus death may occur in 8 to 24 hours in the first stage or in 2 to 14 days in the second stage, with an average time of about 6 days.

The appearances at necropsy vary according to the time of survival, *Morbid anatomy* which depends on the dose of poison taken and the amount absorbed.

When death occurs in the first stage, generally within twenty-four *Death in first stage* hours, there is considerable gastro-intestinal inflammation; the oesophagus, stomach, duodenum, and a variable length of the small intestine show inflammatory reddening and usually some petechial speckling. The changes are most severe in the stomach, which may show superficial ulceration and contain the poison, so that when it is opened it may be luminous if examined in the dark. An odour of garlic may also be noticed, and in severe cases the odour may be detected in the organs generally. Death is due to shock, and the right heart is collapsed.

Death in the second stage occurs from acute necrosis (yellow atrophy) *Death in second stage* of the liver, and the gastro-intestinal inflammation is slight or absent. The body is intensely jaundiced, and patches of purpuric haemorrhage may be evident in mucous and serous membranes and in the skin. The morbid changes are described elsewhere (see LIVER DISEASES, Vol. VIII, p. 106). Intense fatty degeneration is evident in the heart, liver, kidneys, skeletal muscles, and mucous membranes. It is suggested that the haemorrhages result from damage to the blood-vessels from fatty change. The heart is flabby and diffusely pale, and fatty change is *Heart* evident microscopically as a fine fatty vacuolation. The kidneys are *Kidneys* pale, and the cortex is swollen. Fatty degeneration is manifest in the cells of the first convoluted tubules and the ascending loops of Henle. Fatty casts may be seen in the collecting tubules and in the urine. The

- Liver* fatty degeneration of the liver is usually associated with a considerable increase in size when death occurs within a few days of the onset of jaundice. When death is delayed longer, the liver shows much reduction in size and great bile-duct proliferation. Death in these cases occurs in cholaemic coma, and the brain shows slight oedema. (See also JAUNDICE, Vol. VII, p. 267.)
- Symptoms* Owing to the slow rate of absorption of the poison, usually 2 to 8 hours elapse between taking the poison and the onset of symptoms, and indeed the symptoms associated with the first stage of poisoning may be entirely absent. As a rule they are definite and severe but only rarely fatal. At the time the poison is taken a definite taste is noticed, with a sense of warmth in the mouth and throat. After a variable time there follow nausea, vomiting, a burning abdominal pain, thirst, headache, subnormal temperature, and a feeble pulse. Later there may be purging, but this is not constant. The abdomen becomes distended, and the patient is restless and exhausted. The vomit, which may contain blood, is sometimes luminous when examined in the dark. Delirium and convulsions often precede death. This, however, is not the usual result at this stage, and generally after twenty-four hours the patient appears to be approaching convalescence. This period of apparent convalescence may last as long as six days and is then followed by the second stage.
- Second stage* The first symptoms of the second stage are jaundice, epigastric pain, vomiting, looseness of the bowels with the motions often containing blood, and abdominal distension. On examination the liver is enlarged and tender. There is a pronounced tendency to haemorrhage, with bleeding from the nose and vagina and the formation of purpuric spots. The urine is scanty and contains bile and often albumin and blood. Microscopically, casts are commonly seen and, it is alleged, crystals of leucine and tyrosine. Urea is diminished and ammonia increased. The van den Bergh reaction is biphasic. Fever may be present at first but is variable. The pulse at first is normal but of rather low tension and later becomes rapid, feeble, and irregular. The cases are nearly always fatal, death taking place in 2 to 12 days, with an average of about six days. In the recorded cases the descriptions of the size of the liver vary; in some cases the liver was enlarged and in others small. The liver is probably always enlarged at first, and, should the patient die in a short time, an enlargement will be found at necropsy. On the other hand, if the patient lives for a week to ten days, the liver will be small. It is stated that in the late stages of some cases of phosphorus poisoning severe nervous symptoms occur, e.g. violent delirium, convulsions, and paralyses. These are probably associated with haemorrhage in the brain or the spinal cord.
- If the patient is seen when some of the poison is probably still in the stomach and intestine, i.e. within the first thirty-six hours, active measures should be taken to remove the poison as rapidly as possible. Gastric lavage with large quantities of potassium permanganate solution, 1 in 500, should be performed, followed by a similar lavage a few

hours later. Active purgation should be carried out, oily purgatives being avoided, and at the same time a high colonic wash-out should be given. If the stomach pump is not available in an emergency, emetic doses of 10 to 15 grains of copper sulphate may be used. Failing the availability of potassium permanganate, other oxidizing agents may be used, e.g. solution of hydrogen peroxide 1 to 3 per cent. When this has been done, the administration of unrectified French turpentine in doses of 30 minims is recommended, but this is rarely available. During the next few days oil and fat must be rigidly excluded from the diet. When jaundice has begun, there is but little to be done, the treatment being largely symptomatic.

(b) *Chronic Poisoning*

This condition is now only of historical interest; formerly it was fairly common among workers with yellow phosphorus, particularly in match factories. The poisonous fumes gained entrance to the system through the lungs, causing chronic inflammation of the gums and later necrosis of the jaw if previous pyorrhoea or caries was present. It affected both lower and upper jaws. Death was due to exhaustion from chronic sepsis, or sometimes, when the upper jaw was affected, to a spread of the infection to the brain.

(7)—Thallium

1524]. The salts of thallium are only met with occasionally: in the preparation of certain grades of optical glass, the production of tungsten lamps, as a rat poison, and occasionally in medicine to epilate hair. The rat poison zelio-corn and zelio-pastes containing 2.1 per cent and 2.8 per cent of thallium salts respectively are fairly extensively used. *Industrial uses*

In medicine thallium acetate is used in doses of 8 mgm. per kilogram of body weight in children under the age of 10 years for epilation of the hairs in ringworm. This method of treatment is not without danger and, owing to the selective action of thallium on nervous tissue and its slow excretion rate, it has wisely been almost abandoned in the treatment of ringworm. *Medicinal use*

(a) *Acute Poisoning*

In doses of 8 to 9 mgm. per kilo of body weight severe symptoms have been known to occur, and it is probable that quantities only slightly in excess of this amount would be likely to prove fatal (Roche Lynch and Scovell). *Fatal dose*

In three cases of mine in which by mistake ten times the normal epilating doses had been given, two patients died in rather less than thirty hours, and the third died in about sixty hours, but in other cases death has been delayed for several days. *Fatal period*

Unless the patient has lived some time, a mild degree of gastrointestinal irritation with petechial submucous haemorrhage is present, and the organs generally show much parenchymatous degeneration. The heart shows much fatty degeneration, often of the 'tabby cat' *Morbid anatomy*

distribution. The liver may be congested, with fatty degeneration most marked in the centre of the lobule. The kidneys are congested, and there is perhaps some fatty change.

Symptoms

There appear to be two groups: (i) a mild form of intestinal disturbance, sore throat, cough, pain in the stomach, sometimes vomiting, and constipation rather than diarrhoea; the symptoms may not appear for some hours; and (ii) nervous symptoms, drowsiness, headache, articular pains, and sometimes effusion into the joints. The cranial nerves may be affected with varying symptoms. Later choreiform movements, peripheral neuritis, and blindness from optic atrophy may occur. Albuminuria is also described. Death often takes place, generally from heart failure. If the patient survives long enough, epilation will occur.

Treatment

The stomach should be washed out with alkaline lotions and sodium thiosulphate solution, and purgation and the intravenous injection of sodium thiosulphate are recommended. Otherwise treatment should be directed to particular symptoms as they arise. The heart should be watched, and stimulants will probably be necessary.

(b) Chronic Poisoning

In Germany several cases of chronic poisoning have been reported. Fatigue, loss of appetite, pains in the knees, epilation, loss of sight, eosinophilia, and lymphocytosis have been recorded.

8.—POISONOUS FUNGI

1525.] Most species of fungi are non-poisonous, but the distinction in some cases between poisonous and non-poisonous species is so difficult that, unless expert knowledge is available, they should be avoided, and only the common field mushroom, *Agaricus (Psallista) campestris*, should be eaten.

Certain species can be eaten with impunity by some persons but not by others. Some species are apparently poisonous when fresh but on keeping lose this property. Some poisonous species become non-poisonous after thorough washing and cooking in water, due no doubt to the removal of the water-soluble toxic agent. These facts account for some of the apparently paradoxical statements made regarding the toxicity of these fungi.

Poisonous fungi may be classified in the following groups: (i) nervous and severe irritant; (ii) severe irritant; (iii) irritant; (iv) haemolytic.

(i) *Nervous and severe irritant.* Among the fungi capable of producing the symptoms described below are *Amanita muscaria* (fly agaric), *Amanita pantherina* (warted agaric), and species of *Clitocybe* and *Inocybe*.

The active principle of the first two species is muscarine, but, although active principles which resemble muscarine have been isolated from the two latter species, it is doubtful if they are identical. It is also probable that these fungi contain other poisonous ingredients.

No figure can be given of the fatal quantity, and death, which is unusual, occurs in 1 to 2 days.

According to Roch the mortality is less than 2·5 per cent, so that but few cases are seen at necropsy. The post-mortem findings are gastro-intestinal irritation with haemorrhage into the gut due to small ulcers. The heart is generally dilated. *Morbid anatomy*

In 1 to 3 hours after eating the fungus the patient is stricken with malaise followed by nausea, retching, and vomiting with great salivation, followed soon by profuse diarrhoea with watery choleraic stools. The temperature is normal, the pulse slow and irregular, and respiration accelerated with perhaps dyspnoea. The urine is scanty. The pupils are contracted. Soon there appears a peculiar delirium, described by the French as *folie muscarinique*, in which the patient is excited, cries out, gesticulates, becomes very violent, and has to be restrained. In about twelve hours this condition passes off and he becomes calm, the gastro-intestinal condition subsides, and the patient passes into a condition of stupor, from which he awakes a few hours later and is convalescent in a few days. Death is unusual and may occur from exhaustion and from paralysis of respiration. *Symptoms*

After gastric lavage and the administration of castor oil, the use of belladonna is advised, but, if the patient is very violent, morphine or a barbiturate is advised instead. If there are signs of collapse, stimulants will be required. In those cases in which the gastro-intestinal symptoms are severe saline should be administered to replace loss of body fluid, to promote elimination, and to restore renal function. *Treatment*

(ii) *Severe irritant*. Among the fungi which may be classified in this group are *Amanita phalloides* (death cap, white or deadly amanita), *Amanita verna*, *Amanita citrina*, the genus *Volvaria*, *Pholiota autumnalis*, and *Hygrophorus conicus*.

Apart from the fact that there appears to be evidence that the toxic agent is not alkaloidal, there is not any satisfactory evidence to indicate the nature of the active principle. No indication can be given of the fatal quantity; but consumption of such fungi in relatively small quantities causes most severe symptoms and even death. Langeron stated that illness from these fungi was characterized by a relatively long incubation-period of 10 to 12 hours, that the duration of the malady was 3 to 6 days, and that death generally occurred in 3 to 10 days. *Fatal period*

Severe gastro-enteritis is present, with haemorrhage into the intestinal wall and swelling of the lymphatic tissue. There is intense fatty degeneration of the liver, even to the extent that is seen in phosphorus poisoning. Fatty degeneration of the other organs, including heart, kidneys, and muscles, has been described. The kidneys also are stated to show a glomerulo-nephritis. *Morbid anatomy*

The illness begins with malaise, colicky abdominal pain, vomiting, and diarrhoea, which are violent and continuous. The vomit and the motions contain blood and mucus. There is great thirst. The patient is *Symptoms*

collapsed and dehydrated, the picture resembling that of cholera. The urine is scanty. In the less serious cases the condition gradually improves, but convalescence is slow.

In the more serious cases the condition alternates with short remissions followed by exacerbations. There are signs of failing heart, cyanosis of the extremities, and severe cramps, particularly in the calves. Often at the end of 36 to 48 hours there is a remission, the patient becoming somnolent, but this commonly ends in death from heart failure, or about the fifth day jaundice appears. The liver is enlarged and tender. Sugar in the urine has been recorded with diminution of the urea content and a corresponding rise in the ammonia content. Purpuric eruptions are seen. Thus there occurs a condition of acute yellow atrophy, the patient generally dying in 3 to 5 days probably before there has been time for the liver to shrink. Consciousness is retained till the end, thus distinguishing the phalloidian syndrome from that due to muscarine.

Treatment

The stomach should be washed out, and copious drinks of water containing an activated charcoal should be given. Copious quantities of glucose-saline together with cardiac stimulants should be injected intravenously. Limousin suggested that the patient should be given the brains and stomachs of rabbits to eat raw, this suggestion being based on the natural immunity of rabbits to these fungi and on the fact that a neurotoxin and an enterotoxin are concerned. He claimed success with this treatment in several cases, but complete gastric intolerance may render it useless (Le Calvé).

(iii) *Irritant*. In this group may be placed *Russula emetica*, *Lepiota helveola* and other species, *Boletus satanus* and other species of *Boletus*, *Lactarius torminosus*, and *Entoloma lividum*. Possibly some of these, if properly cooked, are not poisonous; symptoms in these cases therefore may be due to lack of precautions.

Poisoning by members of this group is rarely fatal, and no details are available about the fatal dose.

Morbid anatomy

As fatal cases are rare, 1 death in 118 consecutive cases, the signs at necropsy are not well known. No doubt a gastro-enteritis will be found.

Symptoms

Symptoms come on rapidly, generally in three hours. Malaise, nausea, vomiting, and diarrhoea are all present. These abate in about twenty-four hours, and the patient recovers.

Treatment

Gastric lavage and the administration of charcoal and of castor oil are probably all that is required. If necessary, saline may be given and heart tonics, but the latter are not usually required.

(iv) *Haemolytic*. In this group may be placed *Helvella esculenta* and *Morchella esculenta*. The former belongs to the group that is stated to be edible if properly cooked and also if placed on the market in dried form. The German Board of Health have called attention to these precautions in a memorandum in 1930.

The toxic agent is helvellic acid, a volatile acid with powerful haemolytic properties. No doubt it is this volatility which renders the fungus

non-poisonous after boiling or drying, and it would seem desirable to use vinegar in the cooking process to aid its expulsion. There may be other toxic agents in the fungus. It is not possible to state a fatal dose. From the few fatal cases recorded it would appear that death takes place in about nine days.

The usual changes are those of acute necrosis (yellow atrophy) of the liver, with haemorrhages and nephritis. *Morbid anatomy*

Symptoms apparently begin in 5 to 7 hours. In most cases the symptoms are gastro-intestinal, with vomiting and violent pain in the abdomen. Diarrhoea does not usually occur. Sometimes there is slight icterus with some enlargement of liver and spleen. The condition soon clears up. In a few cases the jaundice is severe, and the patient becomes wildly delirious and eventually passes into coma with the signs of acute yellow atrophy of the liver. Haemoglobinuria has been recorded, and it is suggested that the symptoms are mainly referable to the haemolytic effect of the toxic helvellic acid. Albuminuria and a tubulo-nephritis have also been described. *Symptoms*

Treatment consists in gastric lavage and the administration of charcoal and a purgative. Injections of glucose-saline may be given if the condition warrants it. When acute necrosis of the liver sets in, the treatment is symptomatic. *Treatment*

9.—ABORTIFACIENTS

1526.] These drugs are commonly divided into emmenagogues and ecbolics. Apart from the fact that in the courts occasionally an attempt is made by Counsel to persuade a medical witness to agree that the drug belongs to the former class, in the hope perhaps that a less serious view be taken, there seems to be but little advantage in this distinction, and, further, it is in the case of some drugs difficult to know into which group to place them. It is well known that some experienced women, as soon as a period is missed, immediately take a quantity of some essential oil, such as pennyroyal, generally in gin, together with some fairly vigorous purgative. Such a dose sometimes produces the desired effect, i.e. onset of menstruation. Since it is impossible to decide whether the case was one of delayed menstruation or of cessation due to an early pregnancy, it is equally impossible to decide whether the drug is an emmenagogue or an ecbolic. *Emmenagogues and ecbolics*

The most convenient classification is as follows: (i) dangerous poisons; (ii) purgatives; (iii) essential oils; (iv) other vegetable drugs; (v) drugs the pharmacological action of which is known to be on the uterus. *Classification*

(i) Among the dangerous poisons used for this purpose are arsenic, mercury, antimony, phosphorus, and even cyanide. These drugs may be dismissed at once; they have no true abortifacient action, and the occurrence of an abortion can only be regarded as an ordinary complication of a serious illness. In fact cases are on record in which death has taken place from such poisons without an abortion occurring. *Dangerous poisons*

In this group the only true abortifacient drug is lead and, successful as it undoubtedly is, it is so only at the expense of the health and often of the life of the taker. The frequent occurrence of abortion among pottery workers in the days when lead glazes were common is probably the origin of the extension of the use of lead salts for this purpose, and the well known use of diachylon plaster (*emplastrum plumbi*) and other compounds of lead has left behind a permanent damage (see LEAD POISONING, Vol. VII, p. 660). This poison is used much less commonly now, owing largely to the restriction of the sale of diachylon and lead salts by the Poisons Rules; but cases occur from time to time from the taking of white lead, paint, and even the soaking of lead piping in vinegar and the drinking of the resulting liquid.

Purgatives

(ii) Purgatives, e.g. croton oil, gamboge, elaterium, colocynth, and aloes, are ingredients of such medicines, although the first two are not in common use. Probably aloes is the commonest, aloes and canella powder (*hiera picra*) and compound pills of colocynth being common forms of the purgative. Aloes in combination with iron, not uncommonly referred to as 'steel', is another form.

Such pills, as well as other drugs to be mentioned, are often sold by disreputable vendors of such compounds at a price which is several hundred times higher than the cost. It is difficult to describe in scientific words exactly how these purgatives act, but undoubtedly they are occasionally successful. In one case a perfectly healthy girl who was about three months pregnant aborted after taking two 4-grain aloes and iron pills with a trace of oil of savin three times a day for two days. It may be that as griping is a well known effect of these drugs, i.e. painful contraction of the smooth muscle, they may on absorption act similarly on the uterus. There is evidence that aloes also causes congestion of the uterus. Iron and its compounds have not any abortifacient effect whatsoever.

Essential oils

(iii) The compilation of a complete list of all the essential oils that have been used for this purpose would be a formidable task, but the commoner oils which have been and still are used for this purpose can be reduced to a moderate list: oil of pennyroyal, oil of peppermint, oil of rue, oil of tansy, apiol, oil of nutmeg, myrrh, oil of savin, oil of lavender, and oil of cinnamon. These oils are not uncommonly taken in gin, with purgatives, and, when taken in medicinal doses or even in doses 2 to 3 times the medicinal dose, do little if any harm. Only very rarely do they cause abortion, but it must be recognized that this may happen.

They must not, however, be regarded as harmless, for severe symptoms and even death have followed excessive doses, at all events so far as some of the oils are concerned. Thus, for example, 240 minims of oil of pennyroyal are recorded as having been fatal, and I know of a woman who was made dangerously ill, but recovered, after a dose of 180 drops of oil of pennyroyal.

Oil of savin is the most toxic of all, and several deaths have been recorded. Most of the cases have followed drinking an infusion of

savin tops, which contain the oil, the active principle. The symptoms are acute gastro-enteritis, with vomiting, often of blood, and a severe toxic nephritis.

(iv) Again, no attempt is made to record all the vegetable drugs which have been used for the purposes of abortion; the following may be mentioned: caulophyllum, yellow oleander (in India), cotton root bark (gossypii cortex), and black hellebore. Other vegetable drugs

The use of these in England to-day is probably uncommon.

Caulophyllum and cotton root bark are stated to be used in America, whereas the use of yellow oleander is limited to India.

(v) Drugs acting on the uterus include quinine, *Hydrastis canadensis*, pituitary (posterior lobe) extract, and ergot. Oxytocic drugs

Quinine is commonly used now for this purpose and, apart from causing discomfort and some illness to the taker, has probably never been followed by fatal results, and seems rarely to achieve its purpose; but experience of abortion in criminal courts shows that from time to time it is effective: in one case 30 to 40 grains taken at one time produced abortion. It is also given in combination with some local interference, such as douching, and there can be no doubt that this combination assists in the expulsion of the products of conception.

The remaining drugs are too well known to require comment here and, owing to the restriction of their sale to the public, are rarely used, unless the abortionist possesses medical qualifications to enable a purchase to be made.

10.—POWDERED GLASS

1527.] Although for convenience this substance is mentioned here, it is not a poison. Its action is purely mechanical, and therefore it might properly be described as wounding. Occasionally cases are recorded in England in which an attempt, generally unsuccessful, to cause grievous bodily harm or to kill is made by the incorporation of fragments of glass in food. In the East this method is commonly used either alone or with some poison on account of the popular belief that when administered with a substance such as arsenic the effects of the latter are enhanced.

Actions for damages are occasionally brought on account of the accidental swallowing of glass in food. For injury to be caused by glass it would appear probable that two things must happen: (i) the particle of glass must be sufficiently large and sharp, and (ii) it must lodge in some part of the intestinal canal, e.g. the appendix. If the existence of the professional glass-eater is admitted, the chance of a piece of glass causing injury must be remote. It is doubtful if powdered glass in a state of fine division is ever injurious; Johns in 1825 recommended two teaspoonfuls to be given to children for worms.

In the same category must be placed powdered diamonds, little used

*Powdered
diamonds*

now on account of expense. For centuries, however, this powder had a great reputation for death dealing, and Benvenuto Cellini, in his autobiography, stated that it had been used in an attempt made on his life. The matter may therefore be dismissed by stating that, should a fragment of glass become lodged in some part of the intestinal canal whereby injury is done or a viscus perforated, there may be a severe illness, which from its complications may prove fatal, but that such an event is extremely unlikely.

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II.—INDUSTRIAL POISONING

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1.-INTRODUCTION

1528.] Knowledge of industrial toxicology began very early in the history of civilization, for physicians of ancient Greece knew that breathing volatilized lead might cause colic and paralysis. In contrast the physician of to-day has to cope with substances which were little more than chemical curiosities twenty years ago, including coal-tar derivatives, chlorinated hydrocarbons, and ketones, some of which are harmless and others so deadly that their use might better be forbidden. Some are absorbed by inhalation, others through the skin; some attack the liver causing toxic jaundice, others the kidneys causing suppression of urine; some affect the blood causing cyanosis, others destroy the bone marrow causing haemorrhagic purpura and aplastic anaemia.

In Great Britain the Factory Department of the Home Office is

engaged constantly in effective and progressive work for the prevention of disease in industry. It numbers on its staff men and women who are among the greatest living authorities on different aspects of industrial hygiene and toxicology. Their profound store of knowledge, constant helpfulness, and unfailing courtesy are not always fully appreciated by industry. Apart from the medical services of the state it is important that medical practitioners should possess the special knowledge and training enabling them to advise the employer how his industry may be carried out in safety. At present, with a few exceptions, it is only the Medical Inspectors of Factories who have this knowledge. No doubt with the growth of this branch of preventive medicine more members of the medical profession will make themselves competent in this interesting work.

The work of the industrial practitioner consists of medical supervision, preventive medicine, and public health within the confines of an industry. His aim is to safeguard the health of the employee and to minimize time lost from work because of sickness or accident. Though one of his functions is treatment, he is mainly employed in an advisory and a preventive capacity. Working in co-operation with managers, workers, engineers, chemists, and architects he has to discover faults in the working environment and devise remedies for them. One of his most interesting duties is to bring into the effective service of industry the discoveries of the research worker.

2.—PREVENTION OF DISEASE IN INDUSTRY

The principles underlying the prevention of disease in industry can be summarized under fifteen headings.

(i) *Protection of the workman by law*

In Great Britain the number of diseases notifiable under the Factory Act (1937) and the Shops Acts and subject to compensation under the Workmen's Compensation Acts (see p. 136) indicates the existence of an alert and enlightened legislature. From 1878 onwards, provisions were made to control dangerous trades by so-called special rules of the Home Office. The early knowledge of industrial diseases was obtained by placing an obligation on the medical practitioner and employer to notify them to the Chief Inspector of Factories. Between 1896 and 1927 anthrax, toxic jaundice, epitheliomatous ulceration, chrome ulceration, chronic benzene poisoning, and poisoning by lead, phosphorus, arsenic, mercury, carbon disulphide, and aniline were made notifiable. The scope of the Workmen's Compensation Acts is wider than that of the Factory Acts as they are intended to cover all cases of sickness of strictly occupational origin, the individual being considered and not merely the conditions under which he works. There are now some thirty-eight scheduled diseases, of which the diseases of miners and dermatitis alone constitute more than 90 per cent of the cases

*Notification
and
compensation*

compensated (see SKIN DISEASES: OCCUPATIONAL DISEASES, Vol. XI, p. 161). New occupational risks constantly arise; asbestosis and dioxan poisoning are examples of dangers recently brought under control. Sometimes great expansion occurs in one trade, as was the case with the manufacture of accumulators from 1922 to 1924 owing to an increase in the use of motor cars and wireless apparatus. Such expansion of an industry makes great demands on those responsible for the prevention of disease in the factories concerned.

(ii) *Medical inspection under State support*

*Medical
examination
on entry*

In Great Britain the workpeople are protected not only by the inspectors of factories under the Factory Act (1937) and the Shops Acts but also by the inspectors of mines under the Mines Acts. Medical examination of entrants into industry, required by law and carried out by certifying surgeons, is very limited in extent and applies only to young persons between the ages of 14 and 16; but it was undoubtedly the forerunner of the much more extensive voluntary medical examination now often undertaken. An increasing number of employers are realizing the advantages of some kind of medical service in the factory. An additional measure of protection applied in many industries is the periodical medical examination of any workers exposed to known risks. This may be at weekly, fortnightly, monthly, or quarterly intervals and may be carried out by the certifying surgeon or an appointed surgeon approved by the Chief Inspector. These examinations are chiefly undertaken in the case of work involving exposure to lead, carbon disulphide, benzene and other fumes in india-rubber works, and to chromic acid in chromium plating.

*Periodical
examinations*

*Early
diagnosis of
industrial
diseases*

After the War 1914-18, a number of medical men were appointed to work as whole-time or part-time works doctors with happy results, but more are needed. They can often detect intoxication before disability is produced; thus examination of the blood for punctate basophilia is of extreme value in the prophylaxis of plumbism and is indeed essential if manifest plumbism is to be avoided. Similarly in the earliest stages of benzene poisoning the platelet and white-cell counts may fall, and before tetrachlorethane poisoning appears the white-cell count may be raised. Facilities should be available for periodical medical examination and for repeated radiographs of the lungs in persons exposed to the risk of pneumoconiosis (see Vol. IX, p. 708).

(iii) *Prevention of dust and fume*

Dangers from dust and fume may be removed by local or general exhaust ventilation. As Sir Thomas Legge emphasized 'unless and until the employer has done everything—and everything means a good deal—the workman can do nothing to protect himself, although he is naturally willing enough to do his share'. Whenever possible exhaust ventilation through hoods must be applied at the point of origin of the dust or fume; this is in use in the manufacture of electric accumulators and of

white lead, and in the manipulation of silica and asbestos, and of carbon disulphide and benzene in india-rubber works. In certain instances general as opposed to local exhaust ventilation is applied; a good example is the ventilation of dope rooms and of cellulose spraying shops, where it is obviously impracticable to apply local exhausts direct to each doping bench or spraying horse.

In dusty lead processes, such as mixing and pasting in the manufacture of electric accumulators and the breaking down of the white-lead stack, the hose-pipe must be used freely to reduce dust to a minimum. The breaking down of white-lead stacks in a dry state must be forbidden, and white lead should be converted direct into an oily pulp without dry grinding. The use of dry sand-paper for the removal of paint must be forbidden, and wet waterproofed sand-paper be substituted. A preventive method widely applied in the mining, metallurgical, and ceramic industries is the substitution of wet methods for the original dry screening, grinding, milling, and mining processes. Dry drilling is the cause of most of the dustiness in mining, and wet drilling, although it does not ensure a dust-free atmosphere, reduces dustiness considerably. In the grinding industries entailing the use of sandstone wheels a continuous stream of water should run over them. In dusty trades respirators should be used when possible, but it is usually difficult to persuade the men to wear them.

Avoidance of dry processes

Respirators

(iv) *Protective apparatus uncontrollable by the workman*

Sir Thomas Legge insisted that in the prevention of disease in industry 'if you can bring an influence to bear external to the workman—that is one over which he can exercise no control—you will be successful; and if you cannot or do not, you will never be wholly successful'. In the case of exhaust ventilation it is usually simple to have the machinery operating the fans entirely outside the workshop. Even so, the protective apparatus may not be fool-proof, as in the case of the workman in a grinding shop who can turn back the hood from his grinding wheel for use as a receptacle for tools, thus making the whole apparatus ineffective.

(v) *Education of the workman as to the nature of the danger*

Sir Thomas Legge insisted that 'all workmen should be told something of the danger of the material with which they come into contact, and not be left to find it out for themselves, sometimes at the cost of their lives'. The factory physician should emphasize the necessity of teaching the workman to take an interest in protecting himself; he should be taught the importance of clean habits in lead works and should be made to understand such matters as the principles of dust suppression. For example, he should recognize that a vacuum-cleaner is used to remove dust from a workshop for his protection and should therefore never be employed with the motor reversed. Cautionary placards and illustrated notices should be used in the work-rooms concerned so that the early lesions of the skin in anthrax and in chrome ulceration are

*Anthrax**Instruction
in artificial
respiration*

familiar to all. To ensure the prompt treatment of anthrax, an individual card has been devised for workers employed in industries exposing them to risk. In case of illness this is presented to the doctor as a hint that the possibility of anthrax should be considered. It is vitally important that men should be trained in safe methods of artificial respiration so that these can be employed promptly in cases of carbon monoxide poisoning. The factory physician must never agree to a scheme in which the workmen are kept ignorant of the poisonous nature of substances handled. In 1917 American workmen were told that trinitrotoluene might indeed explode but was otherwise harmless; this attitude was a distressing obstacle to those who tried to introduce into American plants the safeguards which had been successfully adopted in Great Britain.

*(vi) Cleanliness of work places**Dust
suppression*

In some dangerous trades constant vigilance by a staff of good foremen is necessary. In the manufacture of trinitrotoluene absorption through the skin cannot be prevented unless benches, tools, floors, and walls are kept spotlessly clean. Similarly glaze rooms and dipping rooms in the potteries, accumulator pasting shops, and all rooms in which a dusty lead process is carried on must be cleaned every night to prevent the inhalation of dust of compounds of lead. Where it is impracticable to use a wet process, as for example in the manufacture of litharge, the foremen must see that no dust is raised in shovelling.

*(vii) Bodily cleanliness**Protection of
skin*

Cloak-rooms, washing rooms, mess-rooms, baths, nail-brushes, towels, and soap must be provided by the employers and used in their time. Where absorption is known to occur through the skin, as in the use of aniline, nitrobenzene, and trinitrotoluene, appropriate protective clothing must be worn. If direct contact with the poison cannot be avoided every means must be adopted to protect the skin. The surface which is necessarily exposed may be covered with a bland ointment, dusted with powder, or washed frequently. There is, however, a risk in too much washing of the skin, and care must be taken to use the least irritating cleansers, to avoid scrubbing, and to replace the lost oils of the skin by inunction with an animal fat.

(viii) General hygiene

Certain principles apply to all trades but are of greater importance in the dangerous trades because their neglect may increase the exposure of the worker to the poisons concerned. Measures must be taken to prevent long hours of work, the employment of boys and girls, undue heat from furnaces and steam from tanks, and the use of underground workshops and bad lighting and ventilation. In this country the law requires that every factory or workshop shall be kept clean and free from effluvia, provided with sufficient means of ventilation, and kept at a reasonable temperature. It does not, however, contain any pro-

visions as regards lighting. If domestic conditions were always of the standard required by law for a factory or workshop, the health of the general population would certainly be improved. It is not suggested that the conditions existing in every factory or workshop in Great Britain are by any means perfect, but in the majority a good standard has been attained. During the years 1914-18 it was realized that hygienic surroundings, good ventilation and lighting, facilities for obtaining food at a reasonable cost, and opportunity for rest and recreation were not only good for the worker but to the advantage of the employer. The benefits derived from such improvements have served to stimulate the provision of further facilities for workers to enjoy a healthy life. Except in the special rooms set aside for the purpose, smoking, eating, and drinking must be forbidden in certain works, for example lead works.

*Rest and
recreation*

(ix) *Improvements by chemists*

The simplest method of preventing an industrial disease is to prohibit the use of the responsible toxic substance. The possibility of such prohibition depends on the discovery of an innocuous substance competent to replace the noxious one. In the case of yellow phosphorus, workers in the match industry were completely protected by the introduction of a harmless substitute in phosphorous sesquisulphide, and the substitution of silver salts for mercury in the silvering of mirrors was another example. Chemists have produced a low-solubility glaze which protects the potter from the dust of white lead, and in a similar way paint technologists have protected the painter of metals by the invention of a non-setting red lead. The use of plastic rubber, i.e. rubber in which litharge has been incorporated in a mother batch to the extent of 90 per cent, will abolish the production of lead dust in certain processes in the rubber industry. Extraction with sulphuric acid or oxidation will reduce or completely remove the carcinogenic activity of a mineral oil such as that used in cotton mule-spinning. Substitutes must be found for toxic solvents. Since coal-tar benzene is highly toxic, the works' chemist must choose less toxic solvents, for example petroleum benzene and acetone. Further research is required to find, for example, a harmless substitute for nitrate of mercury in the felting of fur.

*Replacement
of toxic by
non-toxic
substances*

*Plastic
rubber*

*Carcinogenic
oils*

(x) *Improvements by engineers*

Whenever possible mechanical means should be substituted for hand carriage; examples of this are seen in the use of cranes, rails, hoists, travelling belts, covered conveyors and hoppers, and automatic packing machinery. The abolition of hand filling of shells, the substitution of shot-blasting for sand-blasting and of stainless steel for chromium plating, and the use of an enclosed film steam evaporator in the manufacture of silver nitrate are further examples. The invention of electroplating about 1840 led to a great diminution in the incidence of mercurial poisoning because it took the place of water-gilding, in which mercury

Mercury

Lead was volatilized from an amalgam by heat over a fire. An outstanding contribution to the reduction of the risk of lead poisoning was the invention of the wet-pulping method in the manufacture of white lead. Fifty per cent of the white lead manufactured in this country is never handled in the dry state but is converted from an aqueous pulp to an oily paste in closed machines. *Glass* workers' cataract has been minimized by the invention of a glass-bottle making machine producing bottles at the rate of forty a minute and at one-ninth the original labour cost. In iron and steel rolling mills the use of goggles made of Crookes's glass protects the eyes from the fierce heat and glare and so prevents cataract.

(xi) *Knowledge as to portals of entry of toxic substances*

When it is known by what route—respiratory, alimentary, or cutaneous—a poison is absorbed the medical adviser can, in consultation with the employer, indicate on which principles the methods of protection should be based. In most industries absorption through the respiratory tract is of overwhelming importance. Except in very rare instances lead poisoning is not due to eating with unwashed hands. In a few industries absorption through the skin may take place, for example in the handling of aniline, nitrobenzene, trinitrotoluene, nicotine, and lead tetraethyl. The mechanical details which render the workers in a given industry safe from toxic substances must be settled in consultation with engineers.

(xii) *Multiplicity of poisons in a given trade*

A given trade may be dangerous for more than one reason. For example, in the painter's trade lead, turpentine, benzene, and methyl alcohol may all be used, and in the rubber trade benzene, lead, and carbon disulphide. In the leather trade there may be exposure to anthrax bacilli and to carbon dioxide, sulphuretted hydrogen, nitrobenzene, and aniline. A workman may be ignorant of the substances used, or they may be trade secrets. In taking a clinical history, even when the substances are known, it is often difficult to determine which is responsible. The medical adviser must discover the particular department in which a man works; for example, in the rubber trade, if plastic rubber is not used, there is a risk of lead poisoning, but only in the mixing room where oxides of lead are handled. In complicated processes, such as those of dye manufacture, many difficulties may be encountered in an attempt to determine which chemical compound is responsible, for example, in the so-called aniline tumours of the bladder (see p. 178).

(xiii) *Limitation of exposure*

In certain dangerous processes men must not remain for long periods at any one job: in lead smelting and in processes involving exposure to carbon disulphide, nitrobenzene, and trinitrotoluene, short shifts must be enforced. Hours of work must be limited for men working in compressed air or in hot deep mines. The medical supervisor must

make use of all known methods to detect the earliest onset of poisoning by substances such as lead, benzene, and tetrachlorethane.

(xiv) *Selection of immune persons*

Employment of women and of all persons under 18 years of age in certain trades should be forbidden. In gas works and on blast furnaces, where there is a danger of carbon monoxide poisoning, it is better to employ middle-aged men, who are partially protected by their lesser physical activity and slower respiration. The selection and employment of immune persons only is an ideal, the attainment of which must wait on better knowledge. If research could produce satisfactory tests for immunity to various poisons a great deal of suffering and expense could be abolished.

*Employment
of women and
children*

(xv) *Further researches*

It would be idle to suppose that our knowledge of industrial diseases is a finished chapter. Many diseases of occupational origin remain unknown for years, notable instances being asbestosis and spirochaetosis icterohaemorrhagica (Weil's disease). Clearly there must be others still eluding our search. New processes are constantly springing up. In some countries new solvents for rapidly drying paints and varnishes have been allowed to poison men because these substances were not first tested on experimental animals; poisoning by methyl mercuric iodide in the manufacture of fungicides for seeds need never have occurred had inquiry been made beforehand by means of animal experiments. Until 1933 the co-operation of geologists in attacking the problem of pneumoconiosis had not been sought. The petrological microscope rapidly incriminated silicates such as sericite and sillimanite, whereas previously silica had been held solely responsible. Many problems yet remain to be solved. Is the high incidence of malignant disease of the nasal sinuses in workers in nickel related to substances used in their work and is there also a high incidence of lung carcinoma among them? Will the chemist find a suitable substitute for nitrate of mercury in the felting of fur? Will the bacteriologist succeed in producing effective inoculation against spirochaetosis icterohaemorrhagica? What is to be done about Raynaud's phenomenon produced by the use of vibrating tools, including pneumatic drills, rams, chisels, and riveting machines? These and many other problems await solution. We are on the right path but there is a long way to go.

New solvents

*Geological
researches*

*Chemical and
bacterio-
logical*

3.-NOTIFICATION AND COMPENSATION

1529.] Under the Factory Act (1937) and the Shop Acts the notification of eleven disease groups is compulsory upon medical practitioners and must be made to the Chief Inspector of Factories, Home Office, Whitehall. Diseases which are notifiable if occurring in a factory or workshop are as follows: (i) lead poisoning, (ii) phosphorus poisoning, (iii) mercurial

*Factory and
Shop Acts*

poisoning, (iv) arsenical poisoning, (v) carbon disulphide poisoning, (vi) aniline poisoning, (vii) chronic benzene poisoning, (viii) toxic jaundice, (ix) anthrax, (x) epitheliomatous ulceration due to pitch, tar, paraffin, and mineral oil, and (xi) chrome ulceration.

Under the Lead Paint (Protection against Poisoning) Act of 1936 it is compulsory upon medical practitioners to notify lead poisoning contracted by any person employed in connexion with the painting of any building whether or not it is a factory or workshop.

Acute poisoning

Workmen's Compensation Acts

Medical Arrangements Schemes

Certain diseases, namely acute poisoning by carbon monoxide, hydrogen sulphide, trichlorethylene, and benzene, which are sudden in their effects and therefore classed as accidents, must be reported by the employer to the Factory Inspectors. In addition there is a very large group of industrial or occupational diseases which, although not notifiable, are included under the Workmen's Compensation Acts. The diseases subject to compensation include the notifiable diseases and twenty-seven other disease groups. (See also SKIN DISEASES: OCCUPATIONAL DISEASES, Vol. XI, p. 162.) Pneumoconiosis is provided for under the Silicosis and Asbestosis (Medical Arrangements) Scheme, 1931. Five such schemes now exist: (i) Refractories Industries Scheme, (ii) Sandstone Industries Scheme, (iii) Metal Grinding Scheme, (iv) Various Industries Scheme, and (v) Asbestos Industry (Asbestosis) Scheme.

4.—ARSENIC

Two forms of arsenic poisoning

1530.] Industrial arsenic poisoning occurs in two forms: (i) from inhalation of or contact with the dusts of compounds of arsenic, and (ii) from inhalation of arseniuretted hydrogen gas (see p. 163). The symptoms in the two groups bear little or no resemblance to one another. The compounds of arsenic act as local irritants to the skin and mucous membranes. Only rarely is the dose of arsenic large enough to produce the gastro-enteritis so common in the criminal administration of arsenic. Arseniuretted hydrogen, on the other hand, acts as a powerful haemolytic agent, causing haemoglobinuria, anaemia, and haemolytic icterus.

Occurrence of arsenical compounds

Arsenical compounds are met with in the smelting and refining of ores, in the subliming of white arsenic, and in the manufacture of sheep dip (sodium arsenite), Paris green (copper aceto-arsenite), and Scheele's green (cupric arsenite). White arsenic is used as a preservative of hides, skins, and furs, and Paris green as an insecticide for fruit trees. The dusts of the arsenic compounds manufactured in industry are very light so that in processes of sifting and packing, unless these are carried out in closed apparatus from start to finish, the dust is very likely to alight on and remain on the skin.

The skin is affected especially where there are folds, as around the nose and mouth, or where surfaces are moist, as in the axillae or on the scrotum. Here a dermatitis is set up which leads, if not treated, to extensive ulceration; associated with the skin eruption are con-

conjunctivitis with oedema of the eyelids, coryza, dryness of the throat, and hoarseness. In severe cases vomiting occurs but colic is rare. Head-ache and paraesthesiae in the limbs may occur, but wide-spread polyneuritis is rare and motor paralysis is practically never seen. Brown pigmentation of the skin, usually on the temples, eyelids, and neck is present in those who have worked for years in contact with arsenical dusts. In severe cases there may be intense bronzing of the chest, abdomen, and back. The most characteristic lesion produced in the upper air-passages is perforation of the nasal septum, which may be complete in a month from the time of starting work. Once the perforation is complete no further symptoms occur and the worker may be ignorant of the existence of the condition.

Pigmentation

*Perforation
of nasal
septum*

There is a prevalent belief that arsenic is an important cause of industrial cancer. In actual fact, apart from that occasionally following long-continued therapeutic administration, skin cancer due to arsenic is extremely rare. The wide-spread occurrence of arsenic in industry has naturally led to the belief that it is responsible for many other forms of industrial cancer, but all the available evidence is contrary to such a view. In 1820 John Ayrton Paris described arsenic cancer of the scrotum in tin smelters, but his statement that animals may also be affected has never been substantiated. 'It may, however, be interesting and useful', he wrote, 'to record an account of the pernicious influence of arsenical fumes upon organized beings, as I have been enabled to ascertain in the copper smelting works of Cornwall and Wales; this influence is very apparent in the condition both of the animals and vegetables in the vicinity; horses and cows commonly lose their hoofs, and the latter are often to be seen in the neighbouring pastures crawling on their knees and not infrequently suffering from a cancerous infection in their rumps. . . . It deserves notice that the smelters are occasionally affected with a cancerous disease in the scrotum similar to that which infests chimney-sweepers.' Jonathan Hutchinson (1888) first called attention to the carcinogenic properties of arsenic. He described cases of carcinoma of the skin in patients treated by arsenical mixtures for psoriasis and other skin conditions. The fine powder of arsenical compounds which settles on the skin of the industrial worker may give rise to warts on the nostrils, eyelids, lips, ears, and wrinkles of the neck, and, since these compounds of arsenic are carcinogenic, the warts may become malignant.

*Relation of
arsenic to
cancer*

Warts

Cases of cancer of the skin due to occupational exposure to arsenic are seen in hospitals from time to time but they are rare. In 30 years only three have been seen at the London Hospital, two in 1910 and one in 1924 (O'Donovan, 1928). These three patients had been employed for 26 and 20 years in the sheep-dip industry and each developed a squamous-celled carcinoma. The clinical picture of all was made up of pigmentation, keratosis, and single or multiple malignant growths. There were no special sites. Face, abdomen, scrotum, buttocks, clavicle, and lower chest were affected.

*Incidence of
arsenical
cancer*

Preventive treatment

The floors of workrooms and passage-ways should be of cement so as to ensure impermeability, and they should be frequently flushed with water. Workrooms should be well ventilated and hoods connected with a good draught placed over apparatus emitting dust. All poisonous fumes should be condensed and any dust caught removed. Hot processes should be carried out under glass hoods and manipulation of powders in closed glass cabinets. When possible, mechanical methods should take the place of hand labour. Apparatus and receptacles must be strong to avoid breakage. In all processes in which arsenic dust is likely to arise tables should be provided with downward exhaust ventilation. Protection of the workers against the dust of Scheele's green is difficult to secure because, being light, it is blown about readily. Automatic packing is not possible, and the ordinary means of protection by respirators favours sweating and consequent ulceration of the skin. Persons with a moist skin and those who sweat readily are unsuitable for the work and should be excluded. Special working clothes and head-gear, washing accommodation, and towels should be provided. Neither food nor drink should be taken in the workroom, and smoking and the taking of snuff should be prohibited (Balthazard, 1930).

*Exhaust ventilation**Special clothes*

5.—MERCURY

Three types of poisoning

1531.] Mercury poisoning occurs in industry in three forms: (i) from exposure to the vapours of metallic mercury, (ii) from contact, particularly of the skin, with mercury fulminate, and (iii) from exposure to the vapours of methyl mercury compounds. The clinical picture is different in each of these three types.

(1)—Metallic Mercury

Occupations with risk

Occupations giving rise to the risks of exposure to metallic mercury include mercury mining; recovery of the metal from the ore; separation of gold and silver from their ores by means of an amalgam with mercury; manufacture of barometers and thermometers and some types of electric meters and electric lamps; water-gilding, in which an amalgam of gold or silver is applied to the object concerned and the mercury volatilized by heat; manufacture of oxides and salts of mercury, vermilion, and anti-fouling paint; manufacture of surgical dressings containing mercury salts; bronzing of field glasses and photo-engraving; and the felting of fur and the manufacture of hard felt-hats. Mercury vaporizes even at room temperature and, although there is no doubt that it can be absorbed through the unbroken skin, the use of the metal in industrial processes gives rise to poisoning mainly through the respiratory tract. In 1804 there was a fire in a quicksilver mine in Austria and a good deal of mercury vapour escaped into the air and spread over the countryside; 900 persons in the neighbourhood had mercurial tremor and many cows suffered from salivation, cachexia, and abortion. But poisoning can occur from exposure to mercury at ordinary tempera-

Route of absorption

tures. In 1810 a British ship had some mercury containers broken in the hold. As a result all the birds and cattle on board died; 200 sailors had symptoms of mercury poisoning, and three of them died.

The danger in the felt-hat industry arises from the presence in the air of workshops of fine fur which has been treated with nitrate of mercury in the process of felting. The fine hairs which form the fur of rabbits, hares, musk-rats, and beavers are smooth, resilient, and straight. Treatment with some chemical substance which makes them limp, twisted, and rough greatly aids the felting process and many chemicals have been shown to produce such an effect. Among them is an acid solution of mercuric nitrate which is now used in the preparation of hatters' fur in all countries except Russia. *Felt-hat industry*

The symptoms of mercurial poisoning arising in industry are as a rule much slower in onset and more insidious in character than those which result from the continued internal administration of mercury. Further, two characteristic sets of symptoms which are never seen in medicinal cases occur in industrial cases, namely, tremor and erethism. Salivation and tenderness of the gums and mouth are usually early symptoms. The gums are swollen and bleed readily, but it is not easy to distinguish an early mercurial gingivitis from the pyorrhoea of a neglected mouth. Rarely a mercurial line is seen on the gums. It may resemble the blue line due to absorption of lead but some authors state that it is brownish. *Clinical picture*

The most characteristic symptom, though it is seldom the first to appear, is mercurial tremor. It is neither so fine nor so regular as that of thyrotoxicosis. It may be interrupted every few minutes by coarse shaking movements. It usually begins in the fingers but the eyelids, lips, and tongue are affected early. As it progresses it passes to the arms and then to the legs so that it becomes very difficult for a man to walk about the workshop and often he has to be guided to his bench. At this stage the condition is so obvious that it is known to the layman as the 'hatters' shakes'. Charcot held that the tremor was hysterical. Against this is the fact that it cannot be relieved by psychotherapy but often passes away if the patient gives up his work before it has reached a serious stage. Alcoholism greatly favours its development and it is claimed that no total abstainer has ever suffered severely from tremor. *Tremor*

The severe psychic symptoms known as erethism have been rare since silver took the place of mercury in mirror making. The man affected is easily upset and embarrassed, loses all joy of life, and lives in constant fear of being dismissed from his job. He has a sense of timidity and may lose self-control before strangers. Thus if a visitor stops to watch such a man in the factory, he will sometimes throw down his tools and turn in anger on the intruder, saying that he cannot work if watched. Occasionally a man is obliged to give up work because he can no longer take orders without losing his temper, or if he is a foreman he has no patience with the men under him. Drowsiness by day, depression, loss of memory, and insomnia may occur but under modern conditions hallucinations, delusions, and mania are rare. *Erethism*

*Preventive
treatment*

In the manufacture of clinical thermometers and in laboratories where mercury is handled extensively, the benches should be covered with a smooth and impervious surface sloping in such a way as to drain the mercury into a suitable receptacle at the lowest point. The walls and floors should be of impervious material and the floor should be cleansed at the end of each day's work. Thermometers should not be filled without suitable exhaust-ventilation for the removal of mercury vapour. Overalls, mess-rooms, and washing facilities should be provided. The mouth and pharynx should be frequently rinsed with a mouth-wash and the teeth cleaned with a soft toothbrush and a dentifrice. Periodical medical and dental examination can achieve a great deal, especially by emphasis on the proper hygiene of the mouth. Cavities in carious teeth should be filled, sharp angles smoothed, and stumps and teeth irretrievably decayed extracted.

*Felt-hat
industry*

In the furriers' workshops of hatters the technical processes of carotting, drying, brushing, sorting, and packing are carried out; if the fur-cutting shops are small, cheaply built, and badly managed, poisoning will readily arise. But ventilation and spotless cleanliness in such shops cannot eliminate all risks for after the carrotted fur has left the hatters' furriers' workshop it goes through further processes known as blowing, forming, hardening, sizing, blocking, shaping, crown and brim ironing, planking, proofing, stoving, and pressing. It is, indeed, a pity that chemists have not found any efficient substitute for mercuric nitrate in the carotting process for, although cases of poisoning in Great Britain are now negligible, there are many elsewhere. Russia has had the courage to use a potash method, but this produces felt of inferior quality. The Health Organisation of the League of Nations is to take action in finding a remedy for this blot which persists in modern industry.

*Symptomatic
treatment*

Stomatitis must be treated by the use of the toothbrush, mouth-washes, and dental extraction when necessary. A workman affected by mercurial tremor must be removed from his work and abstain from alcohol.

(2)—Mercury Fulminate

*Use in
industry**Workers
exposed to
risk*

Mercury fulminate, $\text{Hg}(\text{O.N.C})_2$, is handled in explosive factories where detonators and percussion caps are made. It is obtained by reaction on alcohol of a solution of mercuric nitrate in nitric acid. The following workers are exposed to risk: fillers, packers, cleaners, cap loaders, pressers, dryers, sievers, mixers, decanters, weighers, and inspectors. In one process wet fulminate of mercury is spread out by hand on cloths placed on a hot table. One end of the cloth is then raised, and the powder tilted to the other end. In a later process the fulminate is passed through sieves of horsehair to obtain the fine powder necessary for the caps. The fine dust falls upon the skin and dermatitis follows. In one department operatives moisten the material with methylated spirit, work it with the fingers, and then press it into moulds. The skin of most of those employed in mixing, drying, filling, and

preparing the composition shows characteristic lesions. The susceptibility of some individuals is such that they cannot stand it for a day, whereas others only suffer in warm weather. As a rule the cases of 'fulminate itch', as they are called in the trade, are slight. Generally the uncovered parts of the body are attacked by an erythema accompanied by intense itching, swelling, and oedema, particularly on the face, eyelids, neck, behind the ears, and on the forearms. Erythematous papules break out on the inflamed areas and may become vesicles, bullae, and pustules. A pustular folliculitis develops often on the hairy parts of the skin. The fulminate may lodge in a crack or abrasion of the skin and act as a corrosive, causing small painful necrotic lesions on the hands, especially the tips of the fingers, which last about a fortnight. The operatives call them 'powder holes'. If the fulminate attacks the knuckles or the roots of the nails ulceration may penetrate to the joint and bone. Exceptionally the whole body is affected. Recovery takes place in from one to two weeks and is accompanied by desquamation. In persons carrying out sieving operations the superficial mucous membranes also are irritated. After staying a short time in the rooms where these operations are carried out slight pricking of the eyes and nose is felt with an inclination to sneeze, and irritation of the throat. The conjunctivae may become very inflamed and similar inflammation may affect the nose and larynx. The teeth of the majority of workers are blackened owing to the formation of mercury sulphide, produced by the action of sulphuretted hydrogen evolved in the processes of decomposition of food in the absence of careful dental toilet.

*Clinical picture**Skin lesions*

In the manufacture of mercury fulminate meticulous attention should be paid to detail in all matters of cleanliness in the entire plant. The gases given off in the preliminary processes should be either condensed or removed to the outer air well above the heads of the workers. Substitution of machinery for hand labour is impossible on technical grounds. In the rooms where the detonators are filled with the composition, the fumes given off as the result of the numerous small explosions should be removed by means of mechanical ventilation. All persons employed should be provided with well fitting overalls, caps, and india-rubber gloves, and if necessary respirators. The face and other parts of the body should not be rubbed with soiled hands. Washing accommodation should be provided close to the workroom, and a separate towel provided for each worker. The hands and arms should be washed before meals and before leaving in a 10 per cent aqueous solution of sodium thiosulphate. In some factories workpeople coming into contact with mercury fulminate are given ointment wherewith to restore softness to the skin after washing. Such ointments contain lanolin, and either sodium carbonate, balsam of Peru, or phenol. Periodical medical examination is important, and in the first instance persons with delicate skins and those who have suffered from skin diseases must be rejected. Periodical dental examination can achieve a great deal, especially by emphasis on the proper hygiene of the mouth.

Preventive treatment

Symptomatic treatment Whenever powder penetrates into the skin through an abrasion or cut, the skin must be carefully washed in a 10 per cent aqueous solution of sodium thiosulphate. For the conjunctivitis a 2 per cent solution of this substance as an eyewash has been beneficial.

(3)—Organic Mercury Compounds

Aetiology Fungicidal dusts containing organic mercury compounds are used extensively in agriculture. They may burn the skin. The methyl derivatives of mercury attack the nervous system in a unique way. Methyl mercury iodide (CH_3IHg) is a typical compound of the series. Seed disinfectants containing organic mercury compounds as their fungicidal basis are used extensively in farming to prevent certain smut diseases of cereals. For some years mercurial derivatives of the phenyl and tolyl series have been manufactured without any mishap worse than an occasional burn on the skin. Four cases have been studied of poisoning by inhalation of methyl mercury compounds (Hunter, Bomford, and Russell, 1939). Salivation, stomatitis, tremor, and erethism were absent but the nervous system was involved in a unique way.

Phenyl and tolyl compounds There was severe generalized ataxy, dysarthria, and a gross constriction of the fields of vision, memory and intelligence being unaffected. In severe cases the patients remained crippled, unable to stand or to speak intelligibly. Rats and monkeys exposed to the vapour of methyl mercury iodide became ataxic. Histological studies showed myelin degeneration in the peripheral nerves and particularly in the posterior roots and dorsal columns.

Methyl compounds

Clinical picture

Preventive treatment In the manufacture of organic mercury compounds elaborate precautions must be taken to prevent contact with the skin or inhalation. The use of gloves and respirators is not enough. The whole process of manufacture, including the final packing of the dusts, must be carried out mechanically in closed apparatus. The farmer should be protected both by warnings that mercurial dressings are poisonous and by schemes whereby he can obtain from the seed merchant seed already dressed. The seed merchant must dress the seed in a completely closed apparatus.

Symptomatic treatment The ataxy and dysarthria of methyl mercury poisoning must be treated by re-educative movements, persuading the patient to walk on chalked lines. An expert in charge of a speech clinic with great patience and the use of a mirror should teach the patient to speak. With great perseverance in some cases the workman may be taught to use knife and fork, a pencil, and even a typewriter.

6.—SILVER

1532.] Silver is not poisonous in the ordinary sense of the word. The dust of the metal or its salts once absorbed becomes precipitated in the tissues in the metallic state and in this form it cannot be eliminated. Reduction to the metallic state takes place either by the action of light

on the exposed parts of the skin and visible mucous membranes or by means of sulphuretted hydrogen in other tissues.

Occupations involving the risk of argyria can be divided into two groups: (i) including workmen who handle a compound of silver, either the nitrate, fulminate, or cyanide which, broadly speaking, give rise to generalized argyria from inhalation and ingestion of the silver salt concerned; (ii) including workmen who handle metallic silver, small particles of which accidentally penetrate the exposed skin giving rise to local argyria by a process equivalent to tattooing.

*Generalized
and localized
argyria*

(1)—Generalized Argyria

Occupations giving rise to generalized argyria include the manufacture of silver nitrate, the wrapping of lunar caustic pencils, Christmas-cracker making, the silvering of glass beads, mirror plating, electroplating, and photography.

*Occupations
with risk*

Schubert in 1895 reported two cases of generalized argyria occurring in glass-bead silverers in Bohemia. Their occupation consisted of stringing the beads together, dipping them into a reducing solution such as lactose, and then sucking a silver compound into them. A small glass tube 3 to 4 cm. long was used for sucking up the silver compound, which consisted of a solution of silver nitrate, ammonia, and potassium hydroxide. Unless very careful, the workers sucked up some of the solution into their mouths, and although they used a saline mouth-wash a bitter taste remained.

*Silvering of
glass beads*

The use of silver fulminate in the manufacture of Christmas crackers involves a risk to the eyes and to the skin. When an operator makes by hand the detonators of the crackers, she takes two narrow strips of card, already sanded and stuck together, applies powdered silver fulminate around the sanded part, and wraps a strip of tissue paper round it to afford protection.

*Christmas-
cracker
making*

Lewin (1886) mentioned one case of generalized argyria occurring in a silver nitrate worker in Berlin who for twenty-five years handled crystals with bare hands. In 1927 Larsen working in Frankfurt investigated five silver nitrate workers showing generalized argyria. In this country generalized argyria occurring in the manufacture of silver nitrate has practically disappeared. In 1935 Harker and Hunter described six cases, five of whom had been occupied in making silver nitrate and the sixth worked in a silver nitrate packing room.

*Manufacture
of silver
nitrate*

The process causing disfigurement in these men was abolished for technical reasons in 1926 and a method substituted which is not only less wasteful but also less harmful to the workmen (see p. 144). Formerly finely divided silver was dissolved in nitric acid in open dishes of porcelain or platinum standing over gas burners. Each dish held 50 ounces of silver and there were as many as thirty of them in one room. The dishes were covered by sloping glass hoods connected with pipes leading to a shaft. No mechanical exhaust system existed. When the acid was poured on to the silver the room was filled with dense fumes. The

burners were lit under the dishes, and when the mixture had evaporated to a certain specific gravity it was poured into other porcelain pans and left overnight. This pouring caused much splashing, against which neither leather nor rubber gloves afforded complete protection. Next day the mother liquors were poured off, leaving the crystals of silver nitrate to dry. The crystals were then broken up, washed with distilled water, and placed in drying ovens. The door of the oven was opened from time to time and the crystals were broken up. This process sometimes caused silver nitrate to spatter over the faces of the workmen. The crystals were then sifted through a fine sieve with the result that fine particles of silver nitrate were present in the atmosphere for long periods.

Clinical picture

Discoloration

Workers affected by generalized argyria are called by their fellow-workers 'blue men'. The face, forehead, neck, hands, and forearms are of a dark slaty-grey colour, uniform in distribution and varying in depth according to the degree of exposure. Pale scars up to about 6 mm. across may be found on the face, hands, and forearms, due to the caustic effects of silver nitrate. The conjunctivae vary from slight discoloration to a deep brown colour, the lower palpebral portion being particularly affected. The posterior border of the lower lid, the caruncle, and the plica semilunaris are deeply pigmented and may be almost black. The finger nails are a deep chocolate-brown colour. The buccal mucosa is slaty-grey or bluish in colour. Very slight pigmentation may be detected in the covered parts of the skin. The toe nails may show a slight bluish discoloration.

Workers who silvered glass beads developed fissures around the lips and in the mouth generally, and the teeth were stated to become black within eight days, gradually to soften, to break to pieces, and to come out painlessly within a few years. The tongue showed the earliest sign of pigmentation. The first discoloration of the skin began three or four years after beginning the work. Christmas-cracker makers first developed conjunctivitis accompanied by pain and laceration, and secondly a permanent pigmentation of the conjunctiva (Bridge).

At necropsy cases of generalized argyria arising in industry show grey pigmentation of the skin, buccal and nasal mucosae, larynx, trachea, bronchi, endocardium, intima of large elastic arteries and great veins, intermediate zone of kidneys, ureters, bladder, testes, epididymes, mesenteric glands, and choroid plexus.

Preventive treatment

It is almost certain that the modern methods used in handling silver compounds in industry have abolished generalized argyria. Now that glass beads are made and silvered by machinery argyria has disappeared from Bohemia (Teleky). Similarly argyria is no longer seen in Christmas-cracker makers.

In the up-to-date manufacture of silver nitrate, silver and concentrated nitric acid are mixed in a closed apparatus on the top floor of the works. The solution of silver nitrate is passed by pipes to the floor below where it is concentrated in an apparatus known as the film steam

evaporator which consists of a series of tubes made of stainless steel, gazetted with steam, and forming a closed system. Its use has entirely replaced the method of evaporation in open dishes which in the past so often caused occupational argyria.

The process of making silver nitrate has not altered since the beginning of the 19th century; as a result of the increase of the photographic industry, however, the work done by the packers has been doubled since 1918. In the weighing and packing room crystalline silver nitrate is made into packets which may contain from 15 to 600 ounces. When the workman shoots the material into bags from a folded piece of paper like a grocer weighing sugar he creates a dust which loads the atmosphere continuously with finely divided particles of silver nitrate.

(2)—Localized Argyria

In localized argyria the workman handles metallic silver, small particles of which accidentally penetrate the exposed skin surface giving rise to small pigmented lesions by a process equivalent to tattooing. The occupations responsible are the filing, drilling, hammering, turning, engraving, polishing, forging, soldering, and smelting of silver. *Occupations with risk*

The left hand is more affected than the right and the pigmentation occurs at the site of injuries from instruments. Many of these, such as engraving tools, files, chisels, and drills, are sharp or pointed and are liable to produce skin wounds. The piercing saw, an instrument resembling a fret saw, may break and run into the worker's hand. If the file slips the worker may injure his hand on the silver article on which he is working; this is especially the case with the prongs of forks. A man drawing silver wire through a hole in a silver draw-plate gets splinters of silver in his fingers. The pigmented points vary from tiny specks to areas 2 mm. in diameter or more. They may be linear or rounded and in varying shades of grey or blue. *Clinical picture*

The use of gloves is usually impracticable. The tattoo marks remain for life and cannot be removed. *Treatment*

7.—MANGANESE

1533.] Manganese is obtained mainly from pyrolusite (manganese peroxide) of which the ores contain 30 to 90 per cent. The metal is little used except in the preparation of manganese steel. The dioxide is the starting point in the manufacture of all manganese preparations. It is much used in the manufacture of dry batteries and in the pottery, soap, and colour industries. *Uses of manganese*

In 1837 Couper described two severe cases of poisoning in men employed in grinding manganese peroxide in the manufacture of bleaching powder. These men had spastic weakness of the lower limbs with an unsteady gait. The arms were less affected, and there were no tremors. This early observation was overlooked, and in 1901 von

Jaksch described three cases resembling disseminated sclerosis in men employed in drying manganese dioxide. In 1919 Edsall, Wilbur, and Drinker published an article on manganese poisoning resulting from inhalation of manganese dust in a separating mill. The first cases recognized in England were reported by Charles in 1922. The men had been exposed to the dusts of manganese ores from nine months to three years and had been incapacitated for work from three to five years.

Cases have been seen from the inhalation of excessive amounts of dust in the grinding, sieving, and packing of manganese ores and in the manufacture of manganese steel in which the manganese is first fused in an electric furnace. Up to 1935 no case had been recognized in the British Isles in the manufacture of dry batteries (Bridge).

Clinical picture

The symptoms and signs include languor and sleepiness, low monotonous voice, mask-like facies, involuntary movements varying in degree from a fine tremor of the hands to gross rhythmical movements of the arms, legs, trunk, and head, cramps in the calves, retropulsion and propulsion, unsteady gait, and occasionally uncontrollable laughter or crying. There is no disability except in the nervous system and although men seriously poisoned are lifelong cripples the condition is not lethal. Susceptible individuals are few. All three of the cases reported by Charles had a history of increasing loss of strength and showed a spastic paralysis of the lower limbs, immobility of the face, and monotonous speech. The men were all alive at the time of writing but were all completely disabled by the spastic paralysis. Charles agreed with others as to the similarity between this form of poisoning and progressive lenticular degeneration, except that in manganese poisoning the condition remains stationary or improves when exposure to manganese dusts ceases.

Resemblance to progressive lenticular degeneration

Histological studies on necropsy material have shown degenerative lesions of the nerve-cells, particularly in the globus pallidus, the lenticular nucleus, and the cordate nucleus. The fact that lesions have been found in the liver makes still closer the connexion between poisoning by manganese and progressive lenticular degeneration.

Experimental poisoning in monkeys

In 1924 Mella produced manganese poisoning experimentally in four monkeys by administering every day for a period of eighteen months manganese chloride by intraperitoneal injection. The animals developed choreic movements, passed into a state of rigidity, and finally developed tremor resembling paralysis agitans. Gross morbid changes were found in three animals in the lenticular nucleus and the liver. These experiments afford an explanation of the symptoms in most of the cases described. The extrapyramidal motor system is clearly picked out by the poison, hence the rigidity, difficult gait, retropulsion, propulsion, mask-like facies, sleepiness, tremor, and uncontrollable laughter.

Manganese poisoning can be prevented by wearing respirators whenever dusts or vapours are encountered. Personal hygiene is important and the worker must wear protective clothing and gloves, since the

occurrence of skin absorption is established. Local exhaust-ventilation should be applied both at the furnaces to remove fumes and at the packing and sieving apparatus to remove dust. These measures are attended with good results, for it has been found that when they were applied in one particular factory they removed all risk of poisoning encountered by the workers over a period of five or six years.

8.—TOXIC GASES

1534.] The effects of toxic gases are best classified on a physiological basis. They include simple asphyxiants, chemical asphyxiants, irritant gases, and inorganic and organo-metallic gases. The irritant gases are potent poisons, and since they are irrespirable workmen exposed to them fly for their lives so that fatalities are rare. Gases such as carbon monoxide and arseniuretted hydrogen are non-irritant, tasteless, odourless compounds and victims exposed to them may be overcome without even suspecting danger. Although intrinsically one gaseous poison may be more toxic than another, a greater rate of volatility may make the less poisonous one the more dangerous. Marvellous rescues are often made by workmen, foremen, and managers, but courage is not enough unless combined with skill, training, and practice.

*Physiological
classification*

Workshops must be adequately ventilated. No person should be allowed to work single-handed in a place where exposure is anticipated. In certain circumstances the worker must wear an apparatus consisting of an oro-nasal mask connected to a hose led out to uncontaminated air (see Fig. 5). Life-belts should be provided for rescue purposes, and a reviving apparatus consisting of a cylinder containing a mixture of 93 per cent oxygen and 7 per cent carbon dioxide with the necessary valves, tubing, flexible bag, and mask. This apparatus should be in charge of not less than three persons, adequately instructed in its use. At least once a month the equipment, especially the rubber parts, should be examined by them, and the workmen should be practised in rescue drill, including artificial respiration and the use of the appliances provided. It cannot be too strongly insisted that respirators designed to protect the wearer against inhalation of dust are of no avail as a protection against toxic gases. Reliance on a folded handkerchief has cost many a rescuer his life. The Schäfer method of artificial respiration has gradually superseded all others; the technique is described in Vol. IV, p. 238.

Prophylaxis

The treatment of victims overcome by the different gases described will vary somewhat with the gas. No mistake will be made if the victim is removed immediately from the source of poisoning and kept quiet and warm. The first and immediate consideration is the restoration of breathing, and the oxygen-carbon dioxide mixture must be administered whenever respiratory difficulty is apparent. Those responsible for rescue

work must be especially warned of the danger of exposing gassed persons to cold and of walking them up and down. They must realize that rest and warmth are essential in treatment and that the patient must be wrapped in dry blankets and provided with hot-water bottles. It is particularly important to keep the victim quiet if the offending



FIG. 5.—Breathing apparatus for use in irrespirable atmospheres; it consists of an oro-nasal mask connected to a hose, the free end of which is led out into uncontaminated air

gas is one of the irritant group, e.g. nitrous fumes, chlorine, and phosgene, until it is certain that pneumonia is not going to follow the exposure.

(1)—Simple Asphyxiants: Carbon Dioxide

Gases like carbon dioxide and nitrogen cause death from simple asphyxia through deprivation of oxygen. Carbon dioxide (carbonic acid gas, CO_2) is a colourless and inodorous gas which is present in small quantities in outside air but in very large quantities in certain gaseous emanations from volcanoes and in grottoes. It is produced in

industry by decomposing the natural carbonates by means of acids, by calcining stone to lime, by burning coke, charcoal, or heavy hydrocarbons, and by the fermentation of sugar. Liquid carbonic acid is sold in cylinders, and solidified carbon dioxide in the form of a white mass like snow is readily obtained by rapid evaporation of the liquid. Carbon dioxide is used in the manufacture of alkaline salts, beer, effervescing drinks, sugar, white lead, and chemical manures; for sterilizing organic liquors; as a fire extinguisher; to produce cold industrially; to preserve perishable products, such as milk, eggs, butter, and raisins; to make freezing mixtures; in histological and medical work; and in the chemical and rubber industries. Danger of exposure to carbon dioxide mainly occurs in mines, tunnels, and caissons, in fermenting vats in breweries, in mineral-water factories, wells, tanks, ships' holds, coke ovens, boilers, and agricultural silos, and at lime kilns. It is often found mixed with more poisonous gases, for example in sewer gas, lighting gas, industrial gases, products of combustion, explosives, and acetylene gas. Under these conditions it may be carbon monoxide or sulphuretted hydrogen, rather than carbon dioxide, which constitutes the main danger.

*Production**Industrial uses**Industrial risks*

The permissible maximum of carbon dioxide in domestic premises is one part by volume to one thousand parts of air. A proportion of 1 to 3 parts per cent of air is considered as directly harmful, though 2 per cent, which was common long ago in the fermenting vats in breweries, did not produce acute symptoms in the workmen employed there. A proportion of 3 per cent suffices to induce dyspnoea with slight headache; if the proportion is from 5 to 6 per cent the dyspnoea is pronounced and accompanied by headache and sweating; a proportion of 10 per cent for a minute only sets up headache, visual disturbances, tinnitus, tremor, and loss of consciousness. The victim of carbon dioxide poisoning rapidly becomes unable to stand and passes into coma. He must be kept warm and treated by administration of a mixture of 93 per cent oxygen and 7 per cent carbon dioxide.

*Clinical picture**Symptomatic treatment*

Generally the mere lowering of a lighted candle into fermenting vats prior to cleaning or into wells and ships' holds would suffice as a precaution, extinction of the light indicating an irrespirable atmosphere. All such operations could be rendered safe by wearing a breathing apparatus consisting of an oro-nasal mask with tube connexion to the outside atmosphere.

Prevention

(2)—Chemical Asphyxiants

Carbon monoxide, sulphuretted hydrogen, and hydrocyanic acid gas act chemically. They have a specific and prompt asphyxiant action and are classified as chemical asphyxiants and not as simple asphyxiants.

(a) Carbon Monoxide

Water gas, power gas, producer gas, and blast-furnace gas may contain as much as 25 per cent of carbon monoxide (CO). This figure is of great importance since air containing more than one part per

thousand entails danger to life. In recent years there has been a great increase in the manufacture and use of these gases for driving gas engines, heating furnaces and boilers, and welding and soldering. Accidents occur amongst workmen on blast furnaces and amongst persons charging, cleaning, and repairing generating plants. Countless other occupations also involve a risk, and even persons working in offices may be poisoned by unsuspected escapes from underground flues.

Clinical picture

Precautions

The initial symptoms include giddiness, a sense of oppression in the chest, and loss of power in the lower limbs, the patient falling to the ground unconscious. Strict preventive measures must be applied, regulating structural conditions in such a way as to obviate unnecessary risk. A competent person should be made responsible for inspecting the plant concerned at stated short intervals. He should see there is no leakage and should be made to keep a signed and dated record of such inspection. No person should be allowed to work single-handed in a place where exposure is to be anticipated and all the precautionary measures enumerated on page 147 observed.

Treatment

Warmth is essential in treatment. The patient should be wrapped in dry blankets and provided with hot-water bottles. Rest is absolutely necessary. The first and immediate consideration is the restoration of breathing, and the second the promotion of warmth and circulation. The use of the oxygen-carbon dioxide mixture is of great value. Henderson and Haggard (1922) showed that the blood of a man gassed with carbon monoxide up to 35 per cent and to a 50 per cent haemoglobin saturation could be brought down to 15 per cent saturation in thirty minutes when the patient inhaled the oxygen-carbon dioxide mixture. The same men, gassed to comparable saturations, were relieved very slowly when oxygen alone was inhaled.

After-effects

After-effects are headache, cough, depression, and prostration. A simple test can be employed to prove the presence of carbon monoxide in the blood. A greatly diluted solution of the suspected sample is compared with that of normal blood similarly diluted. The latter is yellow whereas blood containing even very small traces of carboxy-haemoglobin is pink. When the proportion of carbon monoxide in the blood is more than 40 per cent of saturation spectroscopic examination affords a confirmatory test (see Vol. II, Plate VI, facing p. 499).

(b) Sulphuretted Hydrogen

Sulphuretted hydrogen (hydrogen sulphide, H_2S) is a colourless gas with a nauseating smell. Poisoning may occur when it is present to the extent of one part per thousand of the air breathed but some individuals are susceptible to as little as one part per 10,000.

Hydrogen sulphide is given off in many industrial operations, the chief of which are: the spinning of artificial silk manufactured by the viscose process; the cleaning out of stills in tar works; the manufacture of ammonium sulphate and sodium sulphide; and work in sewers, sugar manufacture, tan-yards, and brewing.

Inhalation of a large dose causes almost instantaneous death, the patient falling dead often without a sound as if struck with a blow. In such cases the poison acts directly on the central nervous system. Hydrogen sulphide does not unite with haemoglobin but forms an alkaline sulphide in the plasma. Inhalation of small doses causes headache, nausea, depression, and conjunctivitis with lacrimation.

Clinical picture

In treatment artificial respiration should be combined with administration of a mixture containing 93 per cent oxygen and 7 per cent carbon dioxide. In prevention strict requirements should be laid down in the case of men entering apparatus such as a tar still where there is reason to fear the presence of the gas. A responsible person should see that workmen, and if need be the rescuers, wear a life-belt with the free end of the rope in charge of two men outside whose sole duty it is to keep watch and to draw out the wearer if he appears to be affected by the gas.

Treatment

(c) *Hydrocyanic Acid*

Hydrocyanic acid (HCN) is obtained from the cyanogen compounds contained in illuminating gas. Where it is manufactured and handled precautions should be taken against its escape. This applies also to chemical laboratories. Some danger occurs in the following procedures: incomplete combustion of organic nitrogen compounds, exposure of cyanides to the air, decomposition of metallic cyanides, gilding and silvering of lace work, stamping of fabrics by means of Prussian blue, manufacture of sulphocyanide and fulminate of mercury, preparation of oxalic acid by treating wood ashes with nitric acid, extraction of phosphoric acid from bones, electro-plating, and the manufacture of soda by the Leblanc process. In view of the wide-spread use of hydrocyanic acid for the fumigation of ships and houses, strict regulations must be enforced in handling it. Permission to enter places which have been fumigated should depend essentially on the ventilation that can be secured (see p. 85). For clinical picture and treatment of poisoning see page 87.

Occupations with risk

(3)—Irritant Gases

Nitrous fumes, chlorine, phosgene, fluorine, hydrofluoric acid, sulphur dioxide, and ammonia all belong to this group. Some of them are very soluble in water and in the body fluids whereas others, such as chlorine, are less soluble. All of them are irrespirable in any but very low concentrations and many cause immediate irritation resulting in coughing and sneezing. The soluble gases, such as ammonia, cause an immediate oedema in the upper respiratory passages whereas the insoluble gases, such as chlorine and phosgene, are more likely to produce a dangerous oedema of the lung which may not be apparent for some twelve to thirty-six hours after exposure.

(a) *Nitrous Fumes*

Nitrous oxide (N_2O), the anaesthetic, is not poisonous though in the absence of oxygen or when oxygen is present in inadequate proportions

Nitrous oxide

*Nitric oxide
and nitrogen
peroxide*

it acts as a simple asphyxiant. Nitric oxide (NO) is oxidized in contact with air to nitrogen peroxide (NO_2 and N_2O_4) forming the well known orange-yellow or reddish-brown fumes, so-called nitrous fumes. These are given off from fuming nitric acid and are formed when the acid acts on organic substances or metals. They are exceedingly dangerous if inhaled in more than minimal quantities. This difference in action between the different oxides is due to the fact that nitrous oxide is inert in contact with the respiratory tract whereas nitrous fumes in contact with moisture form nitric and nitrous acids, which are severe irritants.

Toxicity

Since nitrous fumes can be breathed with only slight inconvenience in concentrations which will cause a fatal oedema of the lungs after an exposure of half to one hour, and since the least concentration of the gas which will provoke coughing is very little less, the margin of safety between appreciation of the risk and exposure to real danger is very small. Moreover, the initial irritation soon passes off and the worker feels well and is in no apprehension that he may be in a critical condition in a few hours. The gas therefore has most treacherous and insidious qualities, and but for the distinctive colour of the fumes and education of the worker more fatalities would occur.

*Effects and
mode of
action*

The effects of nitrous fumes on the lungs are very similar to those of phosgene (see p. 155), which forms hydrochloric acid in the presence of moisture. Both gases affect primarily the more delicate structures of the lower respiratory tract, in particular the alveoli. Nitrates and nitrites are formed by neutralization of the respective acids by the local alkaline secretions and are absorbed. The nitrites so formed cause some systemic effects but these are overshadowed in severe cases by the intense local reaction. This consists of an acute inflammatory extravasation of fluid into the alveoli. The amount of fluid determines the severity of the case, since from the first it interferes with oxygen absorption to an increasing extent and, as it progresses, with carbon dioxide elimination also. Thus in the early stage there is anoxaemia with little increase in the carbon dioxide content of the blood, causing pallor with little cyanosis or respiratory embarrassment. This state of semi-asphyxia with few signs and symptoms is acutely dangerous and explains the sudden deaths following trifling exertion which occur in this stage. As the oedema develops, retention of carbon dioxide causes intense cyanosis and air hunger, followed by grey cyanosis as the heart fails.

*Local
reaction*

*Causes of
death*

*Incidence of
poisoning in
industry*

Most cases of industrial poisoning occur in the manufacture of nitric and sulphuric acids and of explosives and other nitro-compounds and various nitrates, in the dipping of brass and copper articles in nitric acid, and from the breaking or upsetting of carboys of nitric acid. Great volumes of nitrous fumes are also liberated by the slow burning or incomplete detonation of nitro-explosives such as cordite, and in the combustion of other nitrated bodies, for example celluloid. In such circumstances a large number of people may be affected at one

time, as happened in Cleveland, Ohio, U.S.A., in 1929, when over a hundred fatalities occurred after the burning of a hospital store containing a large quantity of radiographic films. Nitrous fumes are often evolved in electric welding, and when this is carried out in confined spaces fatal poisoning has resulted. Similarly in the manufacture of bone meal the use of impure sulphuric acid containing a proportion of nitric acid may have the same effect.

Reduction in the ventilation by closing doors and windows, or overcrowding a work-room with additional plant, may so raise the concentration of fumes as to extinguish a small safety margin. Thus an electrolytic metal-stripping process using weak nitric acid was worked for eight or nine years without accident; during the last two years the number of vats in the room had been increased from six to twelve. The addition of a thirteenth vat resulted in three cases of gassing during the first morning's work.

Sawdust, wood shavings, or other organic material should not be scattered over spilt nitric acid as they increase the evolution of fumes and take fire.

The initial symptoms—irritation of the eyes and throat, cough, tightness of the chest, and nausea—are slight and may pass unnoticed, especially if the concentration of the gas is low. Although a low concentration will probably be perceived on coming from outside, that appreciation is soon dulled, and symptoms may not become obtrusive until after some hours in the dangerous atmosphere. *Initial symptoms*

Usually, however, the presence of the gas has been noted though little attention may have been paid to it at the time. This is an important diagnostic point for the practitioner called in later to the unconscious patient, for the patient may have mentioned the fact to a relative earlier, not because he was feeling really ill but rather because of weariness and a disinclination for any exertion, using it merely as an excuse for resting at home.

The initial symptoms generally disappear on cessation of exposure and a latent period ensues, during which the patient may even return to work. This latent period varies from two to twenty hours; not uncommonly a man finishes his day's work and is at home for some time before acute signs become manifest. *Latent period*

At the end of the latent period signs appear. Their onset may be sudden and precipitated by exertion. Cough, a feeling of constriction in the chest, and difficulty in breathing occur. As the oedema progresses, so do the symptoms; the cyanosis becomes intense, the air hunger is most distressing, and much blood-stained fluid is coughed up. Unconsciousness usually supervenes, although it may be long in appearing, and then the outlook seems hopeless. So long, however, as there are no signs of failure of the circulation with a thin soft irregular pulse and the cyanosis taking on a leaden hue, these patients tend to recover, for the oedema begins to recede on the second day and thereafter is absorbed rapidly. *Onset*

Some victims become delirious; the temperature may be raised two or three degrees, and a general flaccid paralysis may occur. In some the picture when first seen may be that of pallor with a rapid feeble pulse and a tendency to collapse but without cyanosis or breathlessness. Some of the milder cases may exhibit a picture of acute bronchitis with severe cyanosis, and others nausea, abdominal pain, and vomiting.

Diagnosis

The earlier a diagnosis is made and appropriate treatment started, the better the chances of recovery, and, since absolute rest is essential, a protracted examination must be avoided.

Patients may arrive in hospital simulating other diseases, such as pneumonia, acute bronchitis, or cerebral haemorrhage, but if a history can be obtained it is often so characteristic that a diagnosis can be made on that alone. Usually there has been some reference to gas or fumes about the work-room which did not trouble the patient much, then the latent period of some hours, followed by the onset and progressive development of the illness.

Preventive treatment

Measures must be taken to prevent the escape of fumes and to remove them as nearly as possible at the point of origin by localized exhaust ventilation. Danger must be reduced to a minimum by special efforts to remove fumes before repairs to dangerous plant are attempted. Approved types of breathing apparatus must be provided and maintained for use when fumes are noted or apprehended.

When any reddish fumes can be seen, smelt, or appreciated by the conjunctiva or throat there is serious and imminent danger. All workers, except those properly protected, should be removed from the dangerous area immediately. Spilt nitric acid should be hosed away with large quantities of water by men protected by efficient breathing apparatus.

Symptomatic treatment

In patients seen soon after exposure it may be difficult to decide how much risk has been run. In such cases the patients, in spite of protestations that they are now better and able to carry on, should be kept under observation and at rest for twenty-four hours. Other persons with or without symptoms known to have been seriously exposed should be removed to hospital lying flat. Absolute rest is essential; oxygen should be administered as early as possible and continuously, except for the last five minutes in each half-hour, when it may be stopped to observe whether or not the improvement is maintained. If not, the administration should be re-started at once and the routine continued until no adverse effect is noted on temporary cessation. Administration should be by means of a Haldane mask, by nasal catheter, or by other means which will ensure maximal efficiency. The rate of flow should be 3 to 10 litres per minute, the necessary amount being judged by the effect produced. Venesection of patients with purple cyanosis and a full pulse may give much relief to an overloaded right heart but is contra-indicated in patients with pallor or grey leaden cyanosis, thin pulse, and pulse-rate over 100. Rest, oxygen early and continuously, and venesection when indicated are the three essentials.

(b) Chlorine

Poisoning by chlorine (Cl) may occur in the manufacture of alkali and bleaching powder, in the bleaching of flour, in dye works and paper mills, and in the breaking up of cylinders supposed to be empty. Chlorine in the air breathed to an extent of only one part per 100,000 is highly injurious to man. Fatalities in industry are rare, because the fact that the gas is irrespirable is so well known that at a big escape the workers fly for their lives. In prevention, cylinders, when used, should be fixed outside the work-room. Effective ventilation is required, and the men in charge of the plant should be trained in the use of respirators. For clinical picture and treatment see Vol. V, p. 518.

*Precautions**(c) Phosgene*

Phosgene (carbonyl chloride, COCl_2) has been specially studied in connexion with chemical warfare. From two factories in which it was manufactured twenty-seven cases of poisoning were reported in 1917 and sixty-nine in 1918, mainly in workers engaged in repair work. Large quantities of phosgene are used in the manufacture of aniline dyes derived from diphenylmethane. It is also used in chemical industry for transforming into chlorides certain mineral oxides for obtaining anhydrous oxides of certain acids. It is used for preparing numerous other products, such as arsenic trichloride, benzoic acid, and salol. Cases of poisoning occasionally occur in chemical works as a result of accidental leakage.

Industrial uses

In industrial establishments where it is prepared or handled measures must be taken to prevent the escape of phosgene from closed apparatus and from piping. Exhaust plant must be installed for the withdrawal of fumes at their point of origin, and adequate ventilation is essential. For emergency use gas-masks connected through a hose to a supply of compressed air should be installed. Such a hose must be flexible, impervious to oil and petrol, long enough to reach all points of potential danger, and strong enough to be used as a life line if necessary. Frequent change of working clothes is indispensable, since phosgene readily becomes fixed in materials. The skin should be frequently washed, and the mouth rinsed with an alkaline mouth-wash in order to prevent traces of phosgene dissolved in the saliva from causing irritation of the stomach.

Precautions

For clinical picture and treatment of poisoning see Vol. V, p. 519.

(d) Fluorine and its Compounds

Fluorine (F), hydrofluoric acid (HF), fluorides, and organic fluorine compounds all find a use in industry, mainly for etching glass and in the manufacture of artificial fertilizers and refrigerants.

Industrial uses

In the middle of the 19th century many chemists attempted the isolation of fluorine from hydrofluoric acid and more than one paid with his life for handling too often one of the most dangerous of

History of early investigators

known chemical substances. The danger arises from the volatility and extremely corrosive nature of the vapour of the anhydrous acid.

It is said that G. Knox during his early experiments on the electrolysis of hydrofluoric acid lost permanently the use of his voice and that T. Knox nearly died of its effects (Louyet). Humphry Davy wrote that he had suffered much from the dangerous effects of hydrofluoric acid and it is said that he abandoned his attempts to isolate fluorine because of the risk involved. Louyet, who continued the researches of the Knox brothers, described how his own health deteriorated from using the acid, and how it caused him to suffer from cough and haemoptysis. According to Debray the death of Louyet resulted from his work, but no medical details are available. In 1869 Nicklès died from the effects of accidentally inhaling the vapour of concentrated hydrofluoric acid (Gore). In spite of these deaths the search for the fourth halogen went forward. In 1886 Moissan isolated the element fluorine during the electrolysis of a solution of potassium fluoride in anhydrous hydrofluoric acid, in an apparatus made wholly of platinum. In this way was solved one of the most difficult chemical problems of modern times.

Fluorine and hydrofluoric acid

Action on glass

Fluorine is a greenish-yellow gas with a very irritating smell. It is obtained by treating calcium fluoride with sulphuric acid. From the hygienic point of view it does not often play a direct part because in the atmosphere it becomes converted into hydrofluoric acid. The most characteristic property of hydrofluoric acid is that of dissolving and attacking glass, acting energetically on silicon with which it forms silicon fluoride (SiF_4). In industries using processes which give off fluorine the atmosphere contains fluorine, hydrofluoric acid, and silicon fluoride. Hydrofluoric acid is conveyed in barrels, tarred inside, or else in metal receptacles with a leaden bung. Lead or gutta-percha bottles are used for small quantities.

Compounds of fluorine have recently been increasing in importance in industry. Hydrofluoric acid is used for clouding electric-light bulbs, etching glass, pickling metal and wire, and cleaning sandstone and marble. The fluorides enter into the composition of artificial fertilizers, insecticides, and fumigants used in agriculture. Feil recently emphasized the danger of poisoning from hydrofluoric acid in the manufacture of aluminium by the electrolysis of cryolite. Hydrofluoric acid is evolved with hydrofluosilicic acid (H_2SiF_6) in the superphosphate industry, and also in the production of phosphorus by treating bones with sulphuric acid and in the production of hydrogen peroxide.

Owing to their corrosive properties fluorine, hydrofluoric acid, and fluosilicic acid must be handled with every precaution. The worst danger arises from the volatility and extremely corrosive nature of the vapour of anhydrous hydrofluoric acid. The fluorides and fluosilicates have a toxicity corresponding with their fluorine content.

Hydrofluoric acid, even when highly diluted with air, causes an intolerable burning and pricking sensation in the nose, mouth, and eyes. The local caustic action of fluorine is different on the dry skin and on the moist mucosae because in the presence of water fluorine immediately forms hydrofluoric acid. Both substances if inhaled attack the larynx and the trachea, giving rise to burning pain behind the sternum, cough, expectoration, and even haemoptysis. The ultimate result is slow ulceration of the gums, nasal mucosa, larynx, bronchi, and conjunctivae. When strong concentrations of hydrofluoric acid act on the skin a vesicular dermatitis follows. There may be necroses and ulcers which become indurated and take a very long time to heal. Unless handled with extreme care it may get under the finger nails causing great pain, and if a drop comes in contact with this part of the skin prolonged and painful ulceration is produced.

*Clinical
picture*

Cristiani emphasized the possibility of ingestion as a channel of absorption, because fluorine when inhaled adheres to the mucous membranes of the upper respiratory passages. It is then either eliminated or swallowed. When exposure takes place over long periods of time to an atmosphere slightly charged with the vapours of fluorine and hydrofluoric acid it is unlikely that chronic poisoning would occur. Absorption in man of fractions of a gram of fluorine can give rise to nausea and vomiting, abdominal pain, salivation, pruritus, and diarrhoea. With more than one gram these symptoms increase in severity and death supervenes from respiratory paralysis.

Locally applied exhaust ventilation should be used to remove the gases as near to their point of origin as possible. Mechanical methods should be substituted for hand labour wherever this is practicable. Otherwise contact with the dangerous substances should as far as possible be avoided by the use of tools, wearing gloves, and the application to the skin of lanolin. Baths of hydrofluoric acid for glass etching should be hooded and arrangements made for efficient ventilation. In the superphosphate industry precautions must be taken for the withdrawal of gases and fumes from vats, and special care must be taken when these have to be entered. Rules must be enforced as to the wearing of goggles, respirators, gloves, overalls, and protective footwear. Workers must be instructed about the dangerous properties of the gases to which they are liable to be exposed and the precautions to be taken to prevent their escape into the workshop. Pamphlets and posters giving a brief account of the toxic properties of the gases should be posted up and distributed.

*Preventive
treatment*

Any person injured by contact with concentrated hydrofluoric acid should be removed quickly and first aid administered. Immediate treatment is of the first importance. The acid must be diluted with water, either by immersion or by the use of a hose. Compresses of a dilute solution of ammonium acetate should be applied to the part affected for ten minutes. It should then be dried gently with cotton-wool and the surface covered with aseptic dressings. When the eye is affected

*Symptomatic
treatment*

it should be douched with water, holding the eyelid well back. The person who is burned should not be allowed to move the affected part. In the case of the arm a sling should be applied; if the legs are burned a stretcher should be used. When the mouth is affected it should be washed with an alkaline solution and oil applied over the surface. If the acid has penetrated under the nails solution of ammonium acetate should be applied, although its use is painful.

Sodium aluminium fluoride

Cryolite

Cryolite ($\text{AlF}_3 \cdot 3\text{NaF}$) is a rare mineral found in workable quantities only in Greenland. It is a double fluoride of sodium and aluminium containing as much as 54 per cent of fluorine. In the crude state it is mixed with a considerable amount of quartz. In the vicinity of Copenhagen cryolite is crushed and refined for use in the manufacture of aluminium. After the various accompanying minerals are removed the cryolite itself is ground down to a suitable fineness. Rough crushing is done by means of hammers, finer crushing under rollers. Conveyance between departments is carried out partly by mechanical devices, such as worm-conveyors, bucket elevators, and chain transporters. Cryolite is a relatively soft material and, since it is handled dry, every mechanical influence readily causes dust. Crushing, grinding, grading, drying, and all handling of fine-grained material produce dust. The conveyance of dry material throughout the factory buildings results in the dust hazard being communicated more or less to all work-rooms and thereby to all workers in the factory (Roholm, 1937).

Clinical picture

Møller and Gudjonsson examined seventy-eight employees, all of whom had been working in a cryolite factory for more than two years. They complained of loss of appetite, nausea, shortness of breath, pain and stiffness in the back, vomiting, cough, and tiredness. On physical examination the following four distinct lesions were found.

Pneumoconiosis

Pneumoconiosis was present in various stages in half the subjects examined, the diagnosis being based on radiographs of the chest. The conclusion that the disease of the lungs was due to the quartz-laden dust in the factory is unavoidable.

Fluorosis of bones and ligaments

Fluorosis occurs in bones and ligaments. As the radiographic investigations of the lung condition proceeded, it was found that the shadows of the ribs, clavicles, and cervical vertebrae showed unusual density and abnormalities in the bone pattern. In thirty of the seventy-eight patients obvious changes of varying degree and extent were found. In typical radiographs the osseous pattern of the vertebrae is completely effaced and replaced by dense opaque shadows. In a few places the original bone structure shows though the remaining trabeculae are thick, dense, and indistinct. The transverse processes are covered by excrescences which represent calcification in ligaments. Around the intervertebral and costovertebral articulations are calcified shadows resembling osteophytes. The ligaments on the lateral aspects of the vertebral bodies are calcified and show actual bridges between

the vertebrae. The posterior ends of the ribs are covered by excrescences due to calcification of the attachments of the intercostal muscles. The shadows of the ribs show uniform increase of density, the structure of the bone being destroyed in such a way that the outline of cortex and spongiosa completely disappears. There is a pronounced calcification of the costal cartilages, but the articular cartilages are not affected. In the pelvis the pattern of the spongiosa is completely obliterated by dense opaque shadows resembling those seen in osteoplastic carcinomatosis. Along the periphery of the pelvic bones are blunt excrescences corresponding to calcified muscular attachments; the ischiosacral ligaments and the attachments of the adductor muscles are calcified. Such changes in the bones, ligaments, and muscular attachments are probably due to the deposition of calcium fluoride.

A complete examination of the blood was made on all those workers in whom changes in the bones had been found. In fourteen of the fifty subjects examined there was a fall in the number of the red cells. The average figures were: red blood-cells 3,700,000 per c.mm., haemoglobin 77 per cent, colour index 1.02. No primitive red cells nor basophil stippling was discovered. The white-cell count was normal. The general health of the workers was apparently unaffected by the anaemia. *Anaemia*

Nausea, loss of appetite, and vomiting occurred in forty-two of the workers examined. These symptoms are supposedly due to slight corrosion of the mucous membrane of the stomach by hydrofluoric acid liberated from the swallowed dusts of cryolite. They come on acutely shortly after the dusty work is begun. Thus one of the principal managers of the industry, who only visited the factory occasionally, stated that if he stayed more than ten minutes in one of the places where the dust was particularly thick, he was obliged to get out into the open air in order not to be seized with vomiting. All symptoms disappear as soon as the patient gets out into the open air, and after working hours no feeling of discomfort remains. *Gastric symptoms*

Wherever possible manual labour with shovel and wheelbarrow should be replaced by mechanical conveyance through closed pipes or chutes. The grinding processes must be carried out in enclosed apparatus under exhaust ventilation; drying stoves and grading plants must be fitted with dust filters or suction ventilators. Masks should be supplied to the workers, and regular shifts introduced in all the dusty processes. Packing into bags by means of shovels should be forbidden and replaced by automatic dust-free packing machines. Separate dust-free dining-rooms and dressing-rooms should be built and proper facilities for washing provided. *Preventive treatment*

In Great Britain so far workers in fluorspar (calcium fluoride), enamel, and glass have been found free from fluorosis of the bones in cases in which radiograms of the chest have been carried out in the search for pneumoconiosis.

*Organic fluorine compounds**Use in
refrigerants*

The introduction of fluorine-containing refrigerants has stimulated investigations into the toxicity of hydrogen fluoride, fluorochloromethanes, fluorochloroethanes, and fluorochloroethylenes. Machle and Scott (1935) exposed rabbits to sublethal concentrations of hydrogen fluoride and showed that fluorine was stored in the tissues, especially in the bones, the quantities found amounting to as much as ten times the normal. The use of dichlorodifluoromethane in domestic and commercial refrigerating appliances and in air-conditioning equipment for public buildings has the advantage of reducing the risks of explosion but it introduces the possibility of exposure of workmen to the vapours of an organic fluorine compound. Sayers *et al.* (1930) have shown that prolonged exposure of dogs, monkeys, and guinea-pigs to air containing 20 per cent by volume of dichlorodifluoromethane vapour does not lead to any ill-effects. It is therefore probable that the use of this refrigerant involves little risk to the health of the workman.

(e) Sulphur Dioxide

Risk of poisoning from sulphur dioxide (SO_2) exists in the neighbourhood of furnaces, boiler fires, chemical and dye works, in the manufacture of sulphuric acid, and in bleaching and fumigating.

*Clinical
picture*

In persons unaccustomed to sulphur dioxide even a weak concentration produces an acid taste in the mouth, an increased flow of saliva, and irritation of the nasal, ocular, and respiratory mucous membranes. Spasmodic sneezing and coughing may occur. If the action is too severe or too prolonged the bronchi and lungs are attacked with the production of viscid and even blood-stained expectoration. In fatal cases there is great respiratory distress and death occurs from oedema of the lungs. Many serious cases, however, recover.

*Preventive
treatment*

All necessary precautions must be taken in the manufacture of sulphur dioxide to prevent leakage from kilns and apparatus, to ensure intensive condensation of the gas, and to provide an effective ventilating and extracting system in workshops. Individuals should be protected by wearing overalls, and positive pressure gas-masks connected to a supply of compressed air should be available.

*(f) Ammonia**Precautions*

Accidents with ammonia (NH_3) may occur in leakage from refrigerator plants, in the manufacture of ammonium sulphate in gas works, in spilling of strong solution of ammonia, and in breaking up cylinders supposed to be empty. In the manufacture of ammonia closed receptacles only must be used. Efficient exhaust ventilation must be installed over apparatus which give off fumes and vapours. Steps must be taken to prevent the escape of any noxious gas and for thorough concentration of gaseous ammonia. Gases not condensed should be burned and the workshops kept thoroughly ventilated. Chimneys should be high and close supervision exercised over the discharge of waste water. Apparatus and joints should be carefully luted and gases which cannot be dissolved

in water should be condensed in a vessel containing a dilute mineral acid. Refrigerating plants should be isolated from workrooms, and in all plants where any risk is run respirators should be provided and the workers trained in their use.

For clinical picture and treatment of poisoning see p. 76.

(4)—Organo-Metallic Gases

Certain metals and metalloids form poisonous compounds which are encountered in industry. The dangers of nickel carbonyl, arseniuretted hydrogen, and phosphoretted hydrogen are all well known. Trouble from breathing nickel carbonyl is generally the result of an accident, such as a broken pipe line, and does not imply ignorance of toxicology on the part of industry. Arseniuretted hydrogen and phosphoretted hydrogen are not manufactured in industry but are evolved as accidental by-products in other processes. Their presence is therefore difficult to control.

(a) *Nickel Carbonyl*

Nickel carbonyl, $\text{Ni}(\text{CO})_4$, is a compound of nickel and carbon monoxide and was discovered by Ludwig Mond in 1890. It is a clear pale straw-coloured liquid volatilizing at room temperature and solidifying into a crystalline mass of needles at 23°C . When it is heated to 150°C . it is decomposed into its constituents and metallic nickel is deposited. It gives off a peculiar odour like soot which is perceptible when the air contains one part in two million. The flame of a Bunsen burner becomes luminous when the air contains one part in four hundred thousand. By means of nickel carbonyl pure nickel is isolated industrially from its ores by the Mond process.

In 1902, in a factory in which nickel was separated from the ore, thirty-seven cases of poisoning due to nickel carbonyl occurred, two of them fatal (Mott, 1907). This incident brought to light hitherto unsuspected physiological effects of nickel carbonyl, attended by a train of symptoms unlike those produced by any known substance. The factory was new and amply provided with ventilation. Arrangements had been made for the processes to be carried on automatically in a closed apparatus. No serious cases of poisoning took place so long as the automatic working was not interrupted. On two occasions, however, owing to the breaking of a chain it became necessary to substitute hand labour for the automatic arrangements. The break in the continuity of the system allowed escape of nickel carbonyl in gaseous form. The proportion of carbon monoxide was believed to be about 10 per cent. For several years little further trouble was experienced, but between 1922 and 1930 forty-two cases, including two deaths, were reported, all due to escapes during repairs or to fractures of pipes and leaks in joints subsequent to general repairs and cleaning of the plant.

Experimental investigations have shown that the poisonous effects are entirely due to the nickel of the compound and not to the carbon monoxide (Armit, 1907). Rabbits die in sixty-five minutes after breathing

air containing 0.018 per cent of nickel carbonyl, dogs and cats in twelve to fourteen hours. The animals treated by Armit died when their blood contained not more than 0.072 to 0.16 per cent of carbon monoxide and were not poisoned by iron carbonyl, which contains more carbon monoxide than nickel carbonyl. Its peculiar toxicity is due to the fact that nickel carbonyl enters the respiratory tract in gaseous form and then splits up, depositing nickel as a slightly soluble compound in a very fine state of subdivision over the immense surface of the lungs. It there sets up irritation, congestion, and oedema. Some writers have attributed the toxic action of nickel carbonyl to carbon monoxide which can easily be detected in the blood of the victim, rather than to any specific action of nickel. Whether this be so or not the toxicity of nickel carbonyl is much greater than that of carbon monoxide (Hamilton, 1934).

*Clinical
picture*

The symptoms in man come on immediately after the inhalation of the gas and consist of giddiness, slight dyspnoea, nausea, and vomiting, all of which pass off rapidly in the open air. Then after twelve to thirty-six hours the dyspnoea returns, with cyanosis, rise in temperature, and cough, sometimes accompanied after the second day by blood-stained expectoration. The rise in the pulse-rate is not proportional to the rise in the respiration rate, which may reach as high as 60. Abnormal physical signs in the lungs are usually absent. Although at the time exertion causes considerable distress in breathing, there is no permanent disability and most of the men affected are absent from work only for a short time. In fatal cases delirium develops with death on the fourth to the twelfth day. At necropsy extensive haemorrhages are found, especially in the lungs, the corpus callosum, and the spinal cord. The cause of death is usually oedema of the lungs.

*Preventive
treatment*

The escape of gases or fumes must be prevented by carrying on the process in a completely closed system of iron chambers and pipes. Air containing 0.5 per cent of nickel carbonyl is already dangerous. Compressed air should be supplied on each floor of the works and suitable joints provided at frequent intervals for fixing a face-piece and tube through which to breathe air whenever repairs become necessary. The air should be delivered into the face-piece at sufficient pressure to keep out any gas. The workmen should be instructed to test for the presence of nickel carbonyl by holding the blue flame derived from methylated spirit against the air suspected. In the event of a large leak the gas would burn with a yellow flame, and with a small leak a yellow film forms on the surface of the blue flame. This test detects a proportion of one part in 400,000 of air. Workmen should be instructed by word of mouth and by posters about the toxic properties of nickel carbonyl and the great need to take care.

*Test for
presence of
nickel
carbonyl*

(b) Arseniuretted Hydrogen

Arseniuretted hydrogen (arsine, AsH_3), was discovered in 1775 by Scheele. Its toxicity remained unknown until 1815 when Gehlen, a

Munich chemist, in the course of some researches 'inspired a small portion, and at the termination of one hour was seized with continued vomiting, shivering, and weakness which increased until the ninth day, when he died'. Unfortunately this tragic accident is repeated from time to time.

In 1920 K. C. Schierbeck, of Copenhagen, died from arseniuretted hydrogen poisoning during studies made in collaboration with C. Lundsgaard on the mixture of air in the lungs with hydrogen. Usually the hydrogen was prepared from hydrochloric acid and zinc which were both free from arsenic. As a further precaution the gas was washed by passing it through potassium permanganate solution and a sample was tested for arsenic by Marsh's method (Lundsgaard and Schierbeck, 1923). Towards the end of the experiment the workers ran short of arsenic-free hydrochloric acid, and Schierbeck was imprudent enough not only to make use of ordinary laboratory hydrochloric acid in the preparation of the hydrogen but also to neglect to wash the gas and to test a sample for arsenic. The evening on which the experiments were made he had fever, diarrhoea, and copper-coloured jaundice. The urine was red-brown and contained albumin and haemoglobin. The jaundice persisted and within a few days vomiting occurred, the liver became palpable, and the haemoglobin fell from 46 to 31 per cent. His general condition became rapidly worse, dyspnoea was noticed, suppression of urine supervened, and he died on the ninth day after the accident.

The first cases to be reported in industry occurred in 1873 in Germany, in men engaged in desilverizing lead and zinc ores. In an exhaustive monograph on the subject, published in 1908, Glaister, of Glasgow, summarized all the 120 cases which had been reported up to that time. His work remains the best general account of the subject in English. Since 1908 the number of cases recorded has been more than doubled. The majority of cases have been due to the use of acids and alloys or ores contaminated with arsenic. The occupations concerned are the roasting and extraction of mineral ores, pickling and galvanizing of metals, cleaning of acid tanks, the manufacture of bleaching powder and zinc chloride, the manufacture of hydrogen and its use in ballooning, and lastly the making, charging, and using of accumulators. It follows that the workman may absorb the poison in operations in which the possibility of poisoning is not so much as imagined.

*Occupations
with risk*

The possibility that poisoning might arise from the action of water on the arsenides of alkali metals was recognized by Jones (1907) and by Glaister (1908). In 1923 Legge reported two cases of arseniuretted hydrogen poisoning (one of them fatal) from a dross-refining factory in England. A thunderstorm flooded a floor on which bags containing residues from certain refining operations were stored. Two men were employed packing dross at a distance of ten feet from these bags. One was quite unaffected but the other suffered from vomiting, intense coppery jaundice, and suppression of urine, and died. A third man in charge of a drossing furnace some twenty feet away was slightly affected. A sample of a fresh portion of the contents of the bags was

found to contain 1.6 per cent of arsenic, together with lead, tin, antimony, copper, and aluminium. It smelt of sulphuretted hydrogen and when moistened gave off large quantities of arseniuretted hydrogen. In 1931 Bridge gave an account of six cases with two fatalities caused by the damping down to lay the dust of a residue containing a metallic arsenide. He also mentioned three cases which occurred at the same factory earlier in the year and were not reported. In one of the fatal cases traces of arsenic were found in the bones. In 1931 Löning reported eleven cases (with four deaths) which occurred in a tin-refining works at Wilhelmsberg. The patients had been engaged in the process of tin-refining described above and had sprinkled water over the dross to avoid the raising of dust. In 1932 Bomford and Hunter described two cases occurring in London from a similar cause. In the process of tin refining a dross containing aluminium arsenide was watered down while still hot with several cansful of water. Two workmen were affected. Both suffered from haemoglobinuria and haemolytic jaundice with anaemia. Both recovered completely. Twenty-five cases of arseniuretted hydrogen poisoning have been reported in the tin-refining industry, seven of them fatal. The mortality rate of this small series is therefore 28 per cent. It should be noted that this is one of the few industrial poisons which may kill outright.

*Clinical
picture*

In severe cases the first effects of haemolysis occur within six hours, when haemoglobinuria appears. Within twenty-four hours there is jaundice and by the third day anaemia in which the red-cell count may fall below 1,000,000 per c.mm. Death may occur from anuria in those cases in which severe haemolysis causes blockage of the renal tubules with haemoglobin. Mild cases are often mistaken for food poisoning, and are accompanied by nausea, headache, shivering, exhaustion, giddiness, and vomiting. Reports of series of cases have often mentioned that a number of other men were affected but not so severely as to require admission to hospital. It therefore seems possible that a number of cases too mild to present the classical picture of this form of poisoning may be occurring in industry and escaping detection.

*Preventive
treatment*

The first essential in the prevention of this accident in industry is that all concerned, particularly works' managers and certifying factory surgeons, should be fully alive to the danger of the processes involved and to the signs of early and slight poisoning. The workshops should be adequately ventilated and processes known to be risky should be forbidden in confined spaces. Sometimes a breathing apparatus suitable for use in irrespirable atmospheres must be employed. Such an apparatus consists of an oro-nasal mask with tube connexion to the outer atmosphere. The wearer draws fresh air through the tube by his inspiratory efforts and expels the expired air through a valve in the mask. Further, as suggested by Koelsch, a number of bird-cages containing small birds should be hung as near as possible to the work since it is known from experience that the gas affects them before it affects man.

(c) *Dimethylarsine*

The use of Scheele's green (cupric arsenite) in the preparation of artificial flowers and wall-papers has now only historical interest because aniline colours have almost entirely taken the place of arsenic in these processes. When arsenical colours were used, as much as 60 grains per square foot were found in samples of wall-papers examined. The importance of the matter in relation to wall-papers was that such symptoms as coryza, conjunctivitis, gastro-enteritis, and tinglings in the extremities, all suggesting arsenic poisoning, were found to be associated with residence in rooms papered with arsenic wall-papers.

The mould *Penicillium brevicaulis* while growing in the paste split up the arsenic compounds, liberating from them a gas originally thought to be diethylarsine (Biginelli, 1901), but since definitely identified as dimethylarsine $(\text{CH}_3)_2\text{AsH}$ (Challenger, 1935). In 1931 in the Forest of Dean a child died owing to inhalation of dimethylarsine from mouldy walls in a very damp house. The source of the arsenic in this case was coke breeze, a constituent of the plaster of the walls. The use of concrete blocks containing this substance and the deliberate addition of arsenious oxide to cements to increase their rate of hardening are clearly undesirable.

(d) *Phosphoretted Hydrogen*

Phosphoretted hydrogen (phosphine, PH_3), is a colourless gas, heavier than air, with a distinctive and most disagreeable odour like rotten fish. Even 2 parts per 100,000 in the atmosphere is perceptible and 20 parts per 100,000 will quickly cause death. Poisoning may arise in the preparation and use of calcium phosphide for filling certain kinds of flare mines, in the manufacture of acetylene with impure calcium carbide, and even in chemical preparation and handling of phosphoretted hydrogen in the laboratory. Most of the cases recorded have resulted from the carriage of ferro-silicon as badly ventilated cargoes when the persons responsible were ignorant of the nature of the poison evolved.

Between 1905 and 1908 a number of cases of mysterious illness, often with dramatically fatal outcome, occurred in ships and canal boats carrying cargoes of ferro-silicon. The matter was investigated by Copeman (1909) and by Hake (1910). They concluded that grades of ferro-silicon containing from 40 to 60 per cent of silica were the most dangerous. Their work showed that the poisonous substances evolved from ferro-silicon consisted mainly of phosphoretted hydrogen, sometimes accompanied by small proportions of arseniuretted hydrogen and acetylene. They attributed the evolution of these gases to the action of water on calcium phosphide, arsenide, and carbide respectively. They did not make it clear which of the gases they held responsible for the symptoms of poisoning. Subsequent writers have also evaded this question and the cases are often referred to under the heading of arseniuretted hydrogen poisoning.

The chief symptoms are abdominal pain, nausea, vomiting, and severe

Clinical picture

diarrhoea, often followed by staggering gait, convulsions, coma, and death within twenty-four hours. Neither jaundice nor anaemia appears to have been described in any of the reports. In one series of cases, Bruylants and Druyts (1909) found traces of arsenic present in the bodies of all of four cases. It seems probable that phosphoretted hydrogen was responsible for the symptoms observed in most of these cases, if not in all. Since 1909 the only published cases of illness due to ferro-silicon have occurred in Germany (Thiele, 1921). From samples of the ferro-silicon concerned phosphoretted hydrogen alone was obtained.

Preventive treatment

Where exhaust ventilation is installed it should work in a downward direction since the gas is heavier than air. A breathing apparatus should be used which enables the worker to breathe the outside air. Such an apparatus was worn with success in Great Britain during the war of 1914-18 by girls engaged in filling mines with calcium phosphide. The following recommendations suggested by Copeman should be adopted in handling ferro-silicon: breaking up of ferro-silicon into pieces of the size required at the place where it is used; exposure to the air in a sheltered place for a month at least before loading on to ships; prohibition of transport on passenger ships or on the top of the cargo—it should be carried on deck or, if this cannot be managed, in holds carefully ventilated and separated by air-tight doors from living quarters; application of these measures in transport on barges in inland waters; packing cases containing ferro-silicon should have inscribed on them clear particulars concerning the material, such as the percentage of silicon, the date of manufacture, and the place of origin. Where ferro-silicon is stored work should never begin until the room is ventilated. Zangger (1930) recommended that such storerooms should be under lock and key and that no one should be allowed inside without a permit from the person responsible for effective renewal of the air. Masters of ships carrying ferro-silicon should not only take all necessary measures of safety but should also instruct all persons manipulating the product as to the risk.

9.—BENZENE AND ITS HOMOLOGUES

(1)—Sources of, and Toxicity of, Solvents

Sources of benzene

1535.] Benzole is given off during the distillation of coal in a closed vessel, part remaining in the tar and part in the gas. The chief means of recovery is by stripping the benzole from the coke-oven gas, a method which recently has largely superseded distillation of the tar from gas works and coke ovens.

Benzole is graded commercially as crude or refined, according to the percentage which is distilled below 100°C. Commercial benzole is hardly ever pure, and contains traces of xylene, toluene, phenol, carbon disulphide, and many other substances. The three usual com-

mercial types are: (i) commercial crystallizable 100 per cent benzene (C_6H_6), boiling point $80^\circ C.$; (ii) commercial 90 per cent benzole, which distils below $100^\circ C.$ and contains up to 15 per cent toluol and 2 per cent xylol; and (iii) commercial 50 per cent benzole, which contains 50 per cent of constituents distilling below $100^\circ C.$ and 90 per cent below $120^\circ C.$

Benzole has two more or less distinct fields of application to industrial processes: (i) where it is handled in large quantities in closed mechanical systems, including the distillation of coal and coal tar, the blending of motor fuel, and the chemical industries; and (ii) where it is used as a solvent or diluent, including the rubber industry, artificial leather manufacture, the dyeing and cleaning industry, the manufacture of paints and varnishes, the aeroplane, linoleum, and celluloid industries, and the manufacture of artificial manure, glue, and the extraction of certain alkaloids. *Industrial uses*

Not only are many pure chemical substances obtained from the crude fractions of coal-tar by further distillation and re-distillation, but also by less complex methods mixtures of these substances are obtained which serve most industrial purposes very well. The nature and proportions of these substances contained in any such distillate depend on the source of the distillate, the temperature range within which it has been collected, and the degree to which the remaining impurities have been removed.

It is important to distinguish the original source of a solvent. The distillates derived from the stripping of coke-oven gas or from coal-tar contain mostly aromatic hydrocarbons, of which benzene (C_6H_6) is outstanding in the production of serious chronic toxic effects from damage to the bone marrow. On the other hand the petroleum distillates contain mostly aliphatic hydrocarbons which are relatively harmless. Much experimental work on animals and many clinical observations and pathological reports on man have confirmed this action of benzene, whereas toluene, the higher homologues of benzene, and petroleum distillates containing no benzene have no such action. In the case of these substances the evidence from animal experiments points to stimulation rather than to destruction of the bone marrow. *Source of solvent*
Effects on bone marrow

It is not denied that chronic toxic effects result from continued inhalation of any of these solvents, but chronic effects progressing to a fatal outcome appear to be restricted to benzene. All these substances exert dangerous acute narcotic effects and the outcome may be fatal if they are inhaled in sufficient concentration. For practical purposes, however, under industrial conditions only benzene and mixtures containing benzene produce chronic effects with an ominous prognosis. The benzene content of the industrial solvents is therefore of first importance from the toxicological point of view, for the risk of serious chronic poisoning from inhalation varies, other conditions being equal, directly with this content. *Toxic effects of other solvents*

Benzine is a confusing term: it is usually applied to a petroleum *Benzine*

distillate which contains mainly aliphatic hydrocarbons and little or no benzene. But some commercial benzenes contain as much as 40 per cent of benzene. The terms benzine and benzene have so often been confused in reports of cases of poisoning that the former should be dropped.

Naphtha The terms solvent naphtha and petroleum naphtha refer either to a coal-tar or to a petroleum distillate with a very much higher boiling temperature range than benzole, namely 110° to 190° C., and therefore even the coal-tar product contains either a negligible proportion of benzene or none. The coal-tar derivative is usually called solvent naphtha, whereas the petroleum derivative more usually goes under the name of white spirit.

Toluene Although pure toluene (methyl benzene, $C_6H_5.CH_3$), boiling point 110.4° C., does not contain benzene, commercial toluol may contain an appreciable proportion, up to about 15 per cent, and this may explain serious chronic toxic effects in industrial workers, which have been attributed to the inhalation of toluene.

Xylene The pure xylenes have boiling points of 138° , 139° , and 142.3° C., but commercial xylol has a wider boiling range depending on the standard adopted.

Substitution of other solvents for benzene The greater volatility of benzene as compared with its higher homologues has obvious commercial advantages in aiding quick drying of paints, lacquers, and rubber cements. This is an obstacle to the substitution of benzene by its higher homologues or by petroleum distillates of higher boiling point than benzene. Much, however, has been achieved in this direction in Great Britain, particularly in the rubber industry and in the manufacture of cellulose lacquers, and there is an increasing tendency for manufacturers to state on containers when the product contains either no benzene or less than 15 per cent of benzene.

(2)—Clinical Picture of Benzene Poisoning

Acute poisoning Except for a few cases of accidental or suicidal ingestion, poisoning in industry is due to the inhalation of the vapour of these substances. Acute poisoning is usually the result of breakage of distilling apparatus, cleaning out vats, painting out tanks or other confined spaces with paints containing these solvents, or exposure in some way to the vapours in considerable concentration. All ultimately cause deep narcosis and death if the exposure is continued. Benzene, being the most volatile, is the most dangerous in this respect under industrial conditions, whereas white spirit with its much higher boiling point could only have this effect under exceptional conditions of exposure.

Preliminary stage A preliminary stage of excitement with restlessness, incoherent speech, and flushed face is quite common, particularly with solvent naphtha and benzene. In the case of benzene convulsive movements may occur. With toluene and xylene quiet narcosis is usual. But the use of any one substance alone is rarely necessary in industry, and solvent mixtures containing one or more of the above-mentioned substances together

with a proportion of a totally unrelated solvent, for example, carbon tetrachloride, may be encountered. It should be remembered that there is often a stage of well-being which is followed fairly rapidly by disinclination or inability to move from the surroundings. Muscular exertion and emotional excitement—for example, fear—are believed to increase the severity of the intoxication.

Much that is uncertain and apparently contradictory has been written about the effects of exposure day in and day out to concentrations too low to cause acute effects. This is the result of a number of factors, of which the most important seem to have been confusion in nomenclature of the solvents, uncertainty about the exact composition of the solvent concerned, and a too literal belief that the results of laboratory investigation can be applied without modification to human beings working under ordinary industrial conditions. *Chronic poisoning*

Continued exposure to the vapours of any of this group of solvents will result in depression of the general health with very various symptoms. The minimal exposure required to effect this varies with the individual. Of the early symptoms, headache, either somnolence or insomnia, and mild digestive disturbances are the commonest, then giddiness, nausea and sometimes vomiting, and general weakness. Cessation of exposure and symptomatic treatment will be followed by rapid recovery unless benzene is the cause, in which event there are grave possibilities. *General symptoms*

Benzene destroys the bone marrow and therefore causes a severe anaemia. Although slight anaemia may accompany and form part of the depression in general health associated with long exposure to other members of this group, benzene, under the conditions of exposure in industry, is unique among them in its rapidity of action in many cases and in the intensity of the effect produced. *Destruction of bone marrow*

The victims of industrial poisoning often constitute a small minority of the workers; a single susceptible individual may contract fatal poisoning in an environment which does not give rise even to mild poisoning in others (Ronchetti, 1922). The factors responsible for the great variations in susceptibility are largely unknown, but in general women, especially young women, are more susceptible than men. Changes in the blood may begin from two days to one month after the first exposure, according to the amount absorbed, and they may progress or even develop after exposure has ceased. Death may occur within three weeks of the onset of symptoms. *Susceptibility*

Clinically the picture of chronic benzene poisoning is that of a progressive anaemia with purpura, epistaxis, menorrhagia, and visceral and retinal haemorrhages. Ulcers or gangrenous patches on the lips, fauces, and pharynx are common. Although poisoning may occur only after many years' exposure, there have been fatalities after a few weeks' exposure. Of the original cases reported by Santesson (1897) four of the nine proved fatal within one to four months of the beginning of exposure. When therefore either complaint of the patient or inquiry *Symptoms*

into the exact nature of the work done draws attention to the possibility of exposure to this group of solvents, particularly if there is already a suggestion of anaemia or purpura is noted, or complaint is made of epistaxis, menorrhagia, or other unusual bleeding, the necessity of prompt determination for any exposure to benzene and of immediate examination of the blood is apparent.

*Sequence of
changes in
blood*

Benzene attacks the bone marrow and affects first the platelets, then the granular leucocytes, and finally the red cells. Therefore in the earliest stages of chronic benzene poisoning, when from the practical aspect its detection is so important to everyone, there may be little or no evidence of damage to the red cells but only purpura with leucopenia and granulocytopenia. Even this may be masked temporarily by the influence of a localized septic infection on a bone marrow still capable of responding by the production of a polymorphonuclear leucocytosis. However, the discovery of leucopenia with granulocytopenia suggests inquiry about exposure to benzene and, when there is already knowledge of exposure to solvents in this group, demands exclusion from the work, verification of the presence of benzene in the material used, and examination of others engaged in the same work. The total leucocyte count in chronic benzene poisoning may fall to a very low level; in fact the white cells may almost disappear. A count of 1,000 to 2,000 per c.mm. is common, and a count of 104 has been recorded. In some cases the granular leucocytes fall as low as 10 per cent. The bleeding time may be increased to half an hour, with a corresponding drop in the platelets. The red cell count is reduced, with a corresponding reduction in the haemoglobin percentage. The count may be as low as three-quarters of a million per c.mm., but in many cases a moderate anaemia with a count of three million and upwards may be present. The changes in the appearance of the red cells are slight but anisocytosis, poikilocytosis, and punctate basophilia may occur.

*White cell
count*

*Bleeding
time*

*Red cell
count*

*Morbid
anatomy*

Necropsy usually shows aplasia of the bone marrow. Haemorrhages may be found in the skin, pericardium, pleura, alimentary tract, meninges, bladder, and uterus. Gangrenous stomatitis and even necrosis of the gastric mucosa have been recorded. Benzene cannot be discovered in the body after death.

(3)—Prognosis and Sequelae

*Acute
poisoning*

Acute poisoning by inhalation of any of this group is either rapidly fatal, or recovery is complete in due course. After return to consciousness and apparent recovery at least some days should elapse before return to work, for serious symptoms may return. Headache, giddiness, nervousness, insomnia, nausea, pins and needles in the hands and feet, and general fatigability may persist for a fortnight or more after acute poisoning, and in benzene poisoning respiratory catarrh and pleurisy have also been noted.

The chronic deterioration in general health associated with continued exposure to the members of this group other than benzene soon dis-

appears with removal from exposure and appropriate symptomatic and general treatment. Chronic benzene poisoning is obviously a serious condition. The death-rate is very high but occasionally a severe case ends in recovery.

Hayhurst and Neiswander (1931) have recorded a case in a rubber worker in whom the red cells were 900,000 per c.mm., haemoglobin 10 per cent, white cells 850 per c.mm., bleeding time more than 25 minutes, and the platelets 100,000 per c.mm. Treatment by blood transfusions and iron was followed by recovery, and three and a half years later the blood count was normal except for slight granulocytopenia.

The blood picture may give little indication as to the outcome. When the onset is rapid, the red count well under a million and the white count under 1,000 the victim may recover, whereas a patient with a longer exposure and symptoms for several months with a red count of about three million and without leucopenia may die. Symptoms may develop after cessation of exposure and may be precipitated, as with some other industrial poisons, by an acute infection.

(4)—Diagnosis and Differential Diagnosis of Chronic Benzene Poisoning

The importance of any history of exposure to benzene is self-evident; this, together with leucopenia, granulocytopenia, and thrombopenia, with or without reduction in the red count, should ensure removal from exposure and treatment; the existence of purpura or an abnormal tendency to bleed emphasizes the necessity for prompt action.

Essential thrombopenic purpura and aplastic anaemia both resemble chronic benzene poisoning. Both are of non-occupational origin, but cases show severe anaemia, leucopenia, granulocytopenia, and thrombopenia. Certain other chemical substances used in industrial processes affect the blood, for example dinitrophenol and trinitrotoluene; they cause methaemoglobinaemia with cyanosis and in severe cases jaundice, two conditions which do not occur in chronic benzene poisoning. Aplastic anaemia has been known to occur in industry among persons handling radio-active materials. The use of arsenobenzene and dinitrophenol for therapeutic purposes must be excluded, for both these substances can affect the blood.

*Differential
diagnosis*

(5)—Treatment

The various preventive measures suitable for application in factories and other industrial concerns need not be discussed here. Clearly, however, since benzene is outstanding in this group in its chronic toxic effects, its substitution whenever possible by other solvents which are harmless is the method of first choice. Methods for complete protection against accidental gassing and for the prevention of escape of vapours of any of these solvents into the work-room are necessary. In all processes involving the use of benzene the value of frequent periodical medical

Preventive

*Substitution
by other
solvents*

examination, including examination of the blood, has been proved by experience, especially in the United States. The more complete and effective the prevention of escape of vapours into the work-rooms and the more efficient the daily supervision of the ventilating apparatus, the less is the necessity for periodical medical examination.

Notification Cases of chronic benzene poisoning occurring in Great Britain and believed to be due to work in premises coming under the Factories Acts are notifiable to the Chief Inspector of Factories, Home Office, Whitehall, London.

Symptomatic: resuscitation In acute gassing by any of this group the usual methods of resuscitation are used: rest, warmth, artificial respiration, administration of oxygen and carbon dioxide mixture, and injection of coramine as a respiratory stimulant. Careful watching is necessary because relapses occur; for the same reason and because of the sequelae already referred to, patients should be prevented from returning to work too early.

Return to work In chronic benzene poisoning the patient must be removed from exposure and should not be permitted to return to any work involving exposure to benzole so long as any evidence of the disease remains. When the blood picture cannot be restored to normal the patient should never return to such work.

Blood transfusion Cases of chronic poisoning must be treated by repeated blood transfusions and it must be remembered that the toxic influence may persist even after removal from exposure. The results of treatment are so poor as to convince all who have studied the subject that the use of benzene in industry must be ruthlessly suppressed except where the process used is entirely closed. Fortunately in Great Britain it has been possible to do this and it is rare for more than one or two cases to be notified annually, and in many years no case has been notified.

10.—NITRO- AND AMINO-DERIVATIVES

Chemical composition and biological action 1536.] The coal-tar derivatives are so numerous and complex that it is difficult for the toxicologist to keep pace with the chemists who produce them. The following compounds will be discussed: mononitrobenzene, dinitrobenzene, phenylenediamine, trinitrotoluene, dinitrophenol, and aniline. It is sometimes possible to predict from the chemical composition of the simpler members of the group what their physiological action is likely to be. Addition of a nitro- or nitroso-group usually produces a more toxic compound, but it does not follow that toxicity will continue to increase as more nitro-groups are added. Thus 2-4 dinitrophenol is toxic, whereas trinitrophenol is practically harmless. The position of the substituent groups in the benzene ring has a great effect on the toxic action. Thus the toxic properties of 2-4 dinitrophenol are not shared by any of the other isomers. When a nitro-compound is reduced to an amine, as when nitrobenzene is reduced to aniline or nitrotoluene to a toluidine, the toxic character remains much the same

but the intensity of the action is lessened. Sulphonation renders a compound non-toxic; as soon as aniline is sulphonated it ceases to give trouble. The entrance of chlorine into an aromatic compound does not increase the toxicity as it does in the case of an aliphatic compound. In fact, chlorobenzene is less toxic than benzene.

Sulphonation
Chlorination

Nitrobenzene and aniline act mainly on the blood, converting haemoglobin into methaemoglobin. The symptoms they produce are essentially similar, so that the following subdivision under different headings is to some extent artificial. (See also CYANOSIS, ENTEROGENOUS, Vol. III, p. 520.)

*Methaemo-
globinaemia*

(1)—Mononitrobenzene

Mononitrobenzene (oil of mirbane), $C_6H_5NO_2$, is a liquid used in the manufacture of aniline. It is regarded by experienced men as distinctly more dangerous than aniline. Mononitrobenzene is more poisonous to the nervous system than dinitrobenzene, but the latter has a more destructive action on the blood.

Hamilton (1919) recorded the case of an elderly man who was at work in a soap factory in Boston, carrying a five-gallon can of oil of mirbane. He spilt some of the fluid on his trousers, became shaky and suddenly collapsed spilling more of the fluid on himself. His mirbane-soaked clothing was not removed before he was sent to hospital, and it is not surprising that his condition was serious when he arrived there. He was unconscious with slow irregular breathing but a good pulse. The pupils were small, irregular, and fixed. The skin was a pale grey-blue colour. Some blood withdrawn from a vein was chocolate coloured. Respiration failed but the action of the heart was good until just before death which occurred one hour after admission.

*Absorption
through skin*

Cyanosis

Since nitrobenzene is absorbed through the skin, the victim of such an accident as this should be stripped promptly of his clothes, sponged with weak acetic acid or vinegar, and provided with a shower-bath and clean clothes.

(2)—Dinitrobenzene

Dinitrobenzene, $C_6H_4(NO_2)_2$, is used in the manufacture of dyes. It was the principal explosive used by the Germans in the War 1914-18 and its toxic properties were responsible for 113 deaths in Bavaria from 1915 to 1918. It is solid, and in consequence cases of poisoning develop less rapidly and are less severe than in the case of mononitrobenzene. Poisoning occurs amongst men who either shovel or melt dinitrobenzene. In a mild case there is a sense of pressure in the head which increases to a violent throbbing headache with dizziness and dyspnoea. In severe cases the face is deeply cyanosed; the lips, tongue, and ears are purple; and there are nausea, sometimes vomiting, abdominal pain, a staggering gait, and extreme weakness. An attack seldom occurs during work; a man is more usually overcome some hours after he has left the plant.

*Use as
explosive*

Cyanosis

The main effect of dinitrobenzene is the conversion of oxyhaemoglobin

Blood changes

into methaemoglobin. The blood may be chocolate coloured and sometimes it is possible to detect the bands of methaemoglobin spectroscopically (see Vol. II, Plate VI, facing p. 499). Malden described the blood changes in twenty-one men engaged in the manufacture of dinitrobenzene. The red cells were considerably reduced in numbers and constantly showed marked basophil granulation. The haemoglobin was proportionately decreased, the colour index being normal. The total white cells were increased but with a considerable relative decrease in the polymorphonuclear cells. Methaemoglobin, haematoporphyrin, haemoglobin, and even albumin have been found in the urine. The smoky colour of the urine may be noticed by the men themselves soon after their first contact with nitrobenzene or aniline. Only very rarely does toxic jaundice occur.

Absorption through skin

In 1901 White and Hay carried out experiments proving conclusively that the main channel of absorption of dinitrobenzene is through the skin. In Great Britain before the War there were only two or three factories making nitro-derivatives of benzene, and about as many making use of them in the manufacture of explosives. The factory where the manufacture was on the largest scale gave rise to more anxiety than any other in the country (Legge, 1916). The reason was that there was not sufficient other employment to allow work on dinitrobenzene to be alternated with work not involving such contact. One factory had to close down altogether during a hot summer, because there were not enough healthy men left to carry on the work.

Ventilation

Legge (1916) described another factory where, as a result of overtime, hot weather, and inadequate ventilation twenty-eight cases of illness with two deaths occurred in the course of a few weeks. With reduction of contact to four hours a day the symptoms disappeared. Thus a useful preventive measure is to reduce the dose of the poison. It is well known that cases of poisoning are more frequent in hot close weather than during the colder seasons of the year. Persons under 20 and over 50 seem to succumb sooner than those between 30 and 40 years of age. Lack of care and unclean habits are predisposing causes; those who do not change their working clothes on returning home may sit before the fire and absorb the poison from the evaporation of crystals or from the material in solution on their clothing. Absorption from the alimentary canal is more rapid if the stomach is empty, and it is therefore desirable that men should take a meal before they begin work. Alcohol undoubtedly favours absorption, and several instances are on record in which poisoning has supervened after indulgence in alcohol in ordinary amounts.

*Changes of clothing***(3)—Phenylenediamine**

Phenylenediamine, $C_6H_4(NH_2)_2$, is used for two similar purposes: for dyeing hair black and as a dye for furs. The dye ursol as used commercially is a mixture of the *meta*- and *para*-isomers of phenylenediamine, and it seems likely that the production of aniline in the

tissues is responsible at least in part for the toxic symptoms. It is well known that it may cause dermatitis and sometimes asthma in susceptible persons. In 1929 Mayer and Förster examined 181 persons employed in the fur trade in which *para*-phenylenediamine was used as a dye and found that 111 had suffered from dermatitis or asthma. Its systemic effects are much rarer and have received less attention.

*Dermatitis
and asthma*

Nott fully described a remarkable case of systemic poisoning in the proprietor of a hairdressing saloon. This patient had suffered for three years from attacks of weakness and vomiting sometimes followed by unconsciousness. After a night's rest the effects disappeared. He was seen in a severe attack, when his face was cyanosed and swollen. The lips were violet, the tongue swollen, and the gums purple. The patient had been applying phenylenediamine for a considerable time, and after three months' avoidance of exposure to the dye he had no further symptoms.

Cyanosis

Israëls and Susman (1934) recorded the death of a girl aged twenty-one who for five years had worked in a hairdressing department as a dyer. She used phenylenediamine and was provided with rubber gloves, but after she had applied the dye she had to shampoo the hair, and for this the gloves were removed. At no time had she experienced any affection of the skin directly traceable to the dye. She developed toxic jaundice and died of hepatic insufficiency after an illness lasting seven months. At necropsy the liver was small and showed the changes of subacute atrophy with regeneration nodules. The patient was evidently unusually susceptible to the poison.

*Necrosis
of liver*

(4)—Trinitrotoluene

Before the War (1914–18) little was known about the toxic effects of trinitrotoluene, $C_6H_2CH_3(NO_2)_3$, though indeed in German shell factories four-hour shifts were the rule. The War imposed extraordinary conditions and it was soon found that cyanosis, toxic jaundice, and aplastic anaemia could occur as a result of poisoning. By 1916 at least 25,000 people in Great Britain were employed in shell-filling alone. Work was carried on under the greatest pressure, and men were almost entirely replaced by women. The first symptoms of poisoning by this compound were drowsiness, headache, nausea, loss of appetite, epigastric pain, vomiting, and giddiness. Examination showed some degree of cyanosis of the lips, followed by dyspnoea, with marked drowsiness and staggering gait. Dermatitis in the form of a diffuse erythema often occurred on the dorsal surfaces of the wrists and on the face and neck. The symptoms described either came on gradually after several days' or weeks' work, or they appeared on a hot day after a few hours' work and caused collapse. If cyanosis occurred in one in ten of the workers, toxic jaundice probably affected one in five hundred.

Shell-filling

Symptoms

Dermatitis

Between 1916 and 1919, 407 cases of toxic jaundice were notified and of these 109 died, giving a mortality rate of about 0.05 per cent in all persons handling trinitrotoluene. The greatest incidence of jaundice occurred in the third month of employment. Premonitory symptoms such as drowsiness, giddiness, depression, and dark urine were sometimes present, but the onset was often quite sudden. Sometimes a

*Toxic
jaundice*

Necrosis of liver

latent interval occurred between removal from exposure and the onset of jaundice. Thus a woman who left work owing to an injury developed jaundice five weeks later (Panton, 1917). The intensity of the jaundice varied, and it was sometimes accompanied by irregular fever. The prognosis was always uncertain, but grave symptoms of hepatic insufficiency sometimes appeared rapidly. The mortality rate for all cases was 25 per cent. The morbid appearances were those of yellow and red necrosis of the liver with great reduction in its size and weight (17 to 36 ounces). The necrosis of the liver cells was associated with infiltration and subsequent fibrosis, resembling ordinary portal cirrhosis. There was little attempt at regeneration (Turnbull).

Aplastic anaemia

Aplastic anaemia sometimes occurred among trinitrotoluene workers, but its incidence must have been very small. In 1917 Panton investigated 34 cases of sickness arising among workers handling this substance. Of these 28 had toxic jaundice, 6 had aplastic anaemia, and 4 were examples of a somewhat severe gastric disturbance without jaundice or anaemia. Toxic jaundice and anaemia appeared to be separate and independent pathological states. Anaemia might occur without jaundice and only about 17 per cent of the jaundiced patients became anaemic. The latency of the blood changes was even longer than the latency of the jaundice, for it was found that anaemia could develop as long as nine months after exposure to trinitrotoluene had ceased. The anaemia was usually if not always fatal. At necropsy fatty marrow was found throughout all the bones. There was an excess of iron pigment in the liver and multiple haemorrhages were found in the tissues (Turnbull).

*Absorption through skin**Prevention*

Studies of the precise occupation of those who contracted jaundice (Legge, 1917), together with experimental studies (Moore), proved that the skin was the main channel of absorption. Experience in industry goes to show that when a poison is absorbed by this route the application of preventive measures is most difficult; trinitrotoluene was no exception. By 1918 the risk of poisoning had been greatly diminished not by any single precaution but by the combination of several, of which alternation of employment, periodical medical examination, ventilation, and clean working conditions were the chief. Success was not achieved until mechanical means were substituted for the hand filling of shells, combined with measures of cleanliness which were so precise as to prevent the contamination of the outside of the shells by trinitrotoluene.

Mechanical filling of shells

(5)—Dinitrophenol

As already stated, the 2-4 isomer of dinitrophenol, $C_6H_3OH.(NO_2)_2$, is the one which has toxic properties. These were revealed in the War, especially in French shell-filling factories. The illness begins with lassitude and the worker may notice yellow patches on the covered parts of the skin, due to excretion in the sweat of dinitrophenol. Tremor, excitement, and intense thirst follow, and the face may be slightly

cyanosed. In severe cases orthopnoea, hyperpyrexia, and convulsions set in and death occurs in a condition resembling uraemia. The urine is of an orange-yellow colour and gives a diazo reaction which serves both quantitatively and qualitatively to determine the amount of the poison absorbed, and so to give a clear indication as to when suspension and transference to other work are necessary. The reaction is probably due to the presence in the urine of the reduction product aminonitrophenol. At necropsy no pathognomonic feature is found; there is no atrophy of the liver.

*Urine tests**Necropsy*

In 1918 when it became necessary in Great Britain to use dinitrophenol, the manufacturers profited by the experience in France and took extensive precautions. The men employed were provided with a complete set of underclothing and overalls into which they changed from their working clothes, a separate cubicle being provided for each man. The washing and bathroom facilities were all that could be desired. Well designed exhaust ventilation was applied locally to take away the fumes in the melting of the compound and also in the filling of shells. Any dust that collected around the margin of the shell was removed by a vacuum cleaner. As a result of these measures, combined with daily examination of the urine, little or no trouble was experienced in the use of dinitrophenol, and only one fatal case occurred in England during the War (Legge, 1934).

*Changes of clothing**Exhaust ventilation*

(6)—Aniline

Aniline, $C_6H_5NH_2$, is a colourless oily liquid which darkens on exposure to air or light. It is handled in the manufacture of dyes, in the dyeing and cloth-pressing industries, in the extraction of resin, and in the rubber industry.

Industrial uses

Aetiology

Aniline poisoning arises usually from inhalation, but absorption through the skin and less frequently inhalation of dusts of aniline compounds may cause it. In the descriptions of poisoning by nitrobenzene stress was laid upon the results of carelessness in the splashing of clothes without at once changing them (see p. 173). The same dangers apply in the case of aniline. Equally the breaking of vessels containing aniline and entering chambers filled with its vapour must be avoided. In the absence of efficient locally applied exhaust-ventilation the packing of paranitraniline in powder form may give rise to symptoms. Aniline black dyeing sometimes leads to poisoning.

Routes of absorption

Clinical picture

The symptoms of aniline poisoning are similar in all respects to those of nitrobenzene poisoning. The convenient term anilism may be used to cover the symptoms produced by most of the nitro- and amino-derivatives of benzene. In acute aniline poisoning there is headache, weakness, difficulty in breathing, cyanosis, loss of power in the limbs, and giddiness. In severe cases the cyanosis is more intense and prostra-

Anilism

Recovery tion occurs with a cold moist skin, small pulse, air hunger, and even death in coma. When recovery occurs it is often gradual and may be accompanied by increased frequency of micturition.

Chronic type In chronic poisoning the workers show slight cyanosis, secondary anaemia, and sometimes sleeplessness, headache, giddiness, and abdominal discomfort. In hot weather practically all the men exposed to aniline and similar compounds in a dye works show cyanosis.

Preventive treatment

Closure of apparatus The manufacture of nitrobenzene and the reduction of nitrobenzene and nitrotoluene to aniline and toluidine must take place in closed vessels. Even so escape of small quantities of aniline into the atmosphere is very difficult to prevent unless ample ventilation is provided. Therefore in addition to the technical regulations there must be insistence on cleanliness of the work-rooms, personal cleanliness on the part of the workers, and provision of baths and changes of clothing. Contact with aniline and nitrobenzene especially on the skin, and also the spilling and splashing of these fluids, must be carefully avoided. All workers must be suitably instructed as to the symptoms of nitrobenzene and aniline poisoning and the right steps to take if poisoned. Regular medical inspection of workmen is desirable.

Symptomatic treatment

First aid Workers, and especially those newly employed, must be under supervision in order that assistance may be rendered them on the first signs of poisoning. Medical assistance should be within easy reach. Systematic instruction should be given in first-aid methods and the use of apparatus for oxygen and carbon dioxide inhalation. The possibility of skin absorption must always be borne in mind. A victim whose skin or clothing has been splashed with aniline may turn blue in the face and begin to stagger. Someone may take him out to the fresh air or administer oxygen, when what he most needs is to have his clothes stripped off and be given a bath. Workers entering stills and similar chambers should always be equipped with breathing apparatus and a supply of oxygen. Other aids, such as safety belts which are held by helpers, involve certain risks, especially as the rescuer is easily induced to spring to the assistance of his unfortunate mate without the necessary breathing equipment. The frequency of such accidents calls urgently for the use of breathing apparatus.

Baths
Breathing apparatus

(7)—Aniline Tumours of the Bladder

Workers employed in the manufacture of synthetic dyes sometimes suffer from tumours of the bladder, an association first recorded by Rehn in 1895. At that date the commercial preparation of aniline dyes had been established for some thirty years and had become a flourishing industry, especially in Germany. Rehn discovered three cases of bladder tumour among a group of forty-five men who were engaged in the preparation of fuchsiné, and suggested that the condition followed a

chronic irritation of the mucous membrane of the bladder by certain chemical compounds excreted in the urine over a period of many years. In 1912 Leuenberger published eighteen similar cases from Basle and offered valuable statistical evidence showing that the incidence of this disease was thirty-three times greater among dye workers than among the remainder of the male population. Curschmann undertook a systematic inquiry into all traceable cases of aniline cancer from German dye factories up to 1920 and was able to collect 177 cases. In the British manufacture of synthetic dyes about 40 fatal cases have been recorded. Similar observations have been made in the United States of America, in the Union of Socialist Soviet Republics, and in Austria and Italy. The total number of these occupational tumours so far put on record in the various countries is approximately 550; this does not represent the total incidence.

*Incidence**Other countries*

The manufacture of these dyes involves the use and production of many chemical substances. It is not known which substance attacks the bladder, but it seems to be an amino- not a nitro-compound, and it is most likely *beta*-naphthylamine. It is possible that no one substance is responsible and the following have been accused: aniline, *para*-toluidine, xylidines, naphthylamines, fuchsine, benzidine, and rosaniline. The choice of the name 'aniline cancer' is unfortunate, since it conveys the impression that aniline is the poison responsible for the condition. The term 'amino tumour' has been suggested by Oppenheimer (1926). The difficulties met with in trying to trace the substance really responsible are typical of those found in the investigation of all complex industrial processes. In the dye industry it is very common to have two distinct processes going on in the same room. Further, in the case of a disease with such a long latent period, the workman may have changed from one factory to another or from one department in the same factory to another, each change bringing new compounds into question. Lastly the same compounds used in different processes may be attended with very different degrees of danger. Thus, in making benzidine there may be more actual exposure to aniline vapour than in the manufacture of aniline itself (Hamilton, 1925).

Substances suspected

Hueper, Wiley, and Wolfe (1938) succeeded in producing papillomatosis and carcinomatosis of the bladder in female dogs by daily subcutaneous and oral treatment with *beta*-naphthylamine (from 300 to 450 mgm. daily in capsules) for from twenty to thirty-two months. The lesions observed in cystoscopic and histological examinations of the bladders of twelve of the sixteen dogs thus treated were identical with those seen by these authors in cystoscopic and histological examinations of dye workers. The tumours continued to grow and to become more numerous in some of the dogs after the treatment had been discontinued. In one dog the first neoplasms in the bladder were noted several months after exposure had ceased. Metastatic deposits were not found in necropsies performed upon the dogs, though in one case the carcinoma had invaded the subserosa of the bladder.

Experiments on dogs with beta-naphthylamine

Clinical picture

<i>Cystoscopy</i>	The patient first seeks advice because of haematuria, and cystoscopy reveals a papilloma, sometimes benign, sometimes malignant. Macalpine (1929) pointed out that there is often a premonitory period in which the patient suffers from symptoms of cystitis such as frequency of micturition with strangury. He has found the cystoscopic picture to differ from that seen in septic cystitis in that the mucosa is more brightly red and shows a tendency to mottling. The morbid anatomy and histology of aniline tumours appears to be identical with that of other bladder tumours. Cases showing metastases occur but are not common.
<i>Latent interval</i>	The most usual period of exposure is about twelve years, but tumours have developed in men who had been working in the dye industry from four to twenty-seven years. A number of men may work together for thirty years in a dye factory under apparently identical conditions and, although bladder tumours may arise early in some of them and late in others, the majority never develop any tumours at all. Though there is no doubt that aniline and related compounds can be absorbed through the skin, cases of aniline tumour of the bladder probably arise from absorption through the lungs after inhalation, for members of the clerical staff of dye factories have occasionally been similarly affected.
<i>Mode of absorption</i>	
<i>Preventive treatment</i>	Curschmann (1920) observed that the incidence of bladder tumours diminished considerably in the Frankfurt district after the institution of various protective measures in the factories, such as general cleanliness in the work-rooms, adequate exhaust pipes for the removal of the fumes, mechanical transport of chemical products in closed containers, and various improvements in the personal hygiene of the workmen. Nevertheless bladder tumours still occur in large numbers in the dye industry in various parts of the world.
<i>Curative treatment</i>	Workers should know of the tendency of aniline and its compounds to produce new growths in the bladder. Soon after the discovery of such tumours in 1895 facilities were provided in the Höchst factories for cystoscopic examination of every suspicious case. Credit was due to the management for this step, and similar measures have now been instituted in dye works all over the world. The strongest argument for the routine use of the cystoscope in aniline dye works is that men have remained well for a number of years after cysto-diathermy of a papilloma. Early diagnosis of all cases would ensure removal of every papilloma before it did any harm.

11.—CHLORINATED HYDROCARBONS

1537.] The rapid growth of the moulded plastic and cellulose lacquer industries has led to the extensive use of many new solvents most of which were little more than chemical curiosities before about 1925. Amongst these are the chlorinated hydrocarbons which have flooded

the market largely because the alkali industry requires an outlet for its by-product chlorine. The various members of the group are useful as refrigerants, as degreasers of metals, fire-extinguishers, cleansers of textiles, solvents for rubber, and thinners of cellulose lacquers. They are non-inflammable, non-combustible, and non-explosive, but they are far from harmless in their effects on the human body. The action of carbon tetrachloride has been extensively studied because of its use in hookworm therapy. Tetrachlorethane dramatically attracted attention in the War (1914–18), and a mass poisoning from leaking refrigerators in Chicago has led to an increase in knowledge of the action of methyl chloride. Trichlorethylene has been studied because of its extensive use in dry cleaning.

*Industrial
uses*

(1)—Methyl Chloride

The first cases of poisoning by methyl chloride, CH_3Cl , in industry were reported by Gerbis in 1914. These were two men working in a chemical plant, who suffered from nausea, vomiting, and restlessness followed by somnolence, and then by dimness of vision which did not clear up for fourteen days after leaving work. Subsequently forty-one cases were reported in Switzerland, Germany, and the United States, all of them employed upon making, installing, or repairing refrigerators. The famous Chicago cases described by Kegel *et al.* in 1929 were most of them non-industrial. They recorded twenty-nine cases with ten deaths. Three of the non-fatal cases were industrial. There was a rise of temperature, pulse, and respiratory rate, usually with oliguria and occasionally with suppression lasting up to forty-eight hours. Evidence of acute nephritis was found in about half the cases. Anaemia occurred in some of the men affected, the red cells dropping as low as 3,100,000 per c.mm. and the haemoglobin as low as 50 per cent. Sometimes there was leucocytosis with a normal differential count. So far only one case has been recorded in Great Britain. The affected person, employed by an engineering firm, was engaged in repairing a refrigerator in a private house. The symptoms included giddiness, weakness of extremities, sickness, blurring of vision, and pharyngitis, which incapacitated him for several days (Bridge, 1931).

*Suppression
of urine
Anaemia*

*General
symptoms*

(2)—Carbon Tetrachloride

Carbon tetrachloride, CCl_4 , is used in industry as a solvent for fats and rubber, for dry cleaning, for cleaning oil from machinery, and under the name pyrene as a fire extinguisher. In animal experiments it has been shown to cause necrosis of the liver (Lamson, *et al.* 1929). In man it may attack both liver and kidneys, but in most clinical histories so far published the symptoms of renal injury overshadow those of hepatic injury. The early stages of the illness are characterized by persistent headache, nausea, vomiting, diarrhoea, and tenderness over the liver, but such symptoms are often followed by oliguria, suppression of urine, and uraemia.

*Industrial
uses*

Symptoms

Anaesthetic effects

Deaths in industry from the anaesthetic effects of carbon tetrachloride are seldom encountered, though they have occurred from the use of this substance as a dry shampoo for the hair. Cases of chronic poisoning are not numerous but are rapidly increasing. Boveri (1930) of Milan recorded the case of a young man who worked two days degreasing with carbon tetrachloride in a poorly ventilated room. On the evening of the second day he was suddenly taken ill with vomiting, abdominal pain, and vertigo, followed by suppression of urine and coma. There was then a slight rise of temperature followed by jaundice, but after two months he recovered. Mauro (1930) of Milan reported five cases in men occupied in the preparation of an insecticide containing carbon tetrachloride. Two were poisoned severely, enlargement of the liver, albuminuria, and casts being noted. Subsequently profound diuresis occurred and both patients recovered.

Jaundice

Henggeler (1931) reported six cases of poisoning in one family in Rorschach, Switzerland. For three days the family worked for long hours cleaning and waxing the floors of a large school. The wax, which contained carbon tetrachloride, was first heated by the man and then applied hot by the entire family. All the patients suffered by the end of the third day from nausea, headache, and malaise. The man, however, who had undoubtedly breathed more of the vapour than the others while heating the wax, became dangerously ill with mental confusion, headache, hiccup, nausea, vomiting, diarrhoea, and scanty urine loaded with albumin. At the end of three weeks he was exhausted and emaciated having lost 29 pounds in weight, but he gradually recovered after three months.

In 1932 McGuire reported from Boston seven cases of poisoning among workers passing felt through a warm mixture containing 33.3 per cent of carbon tetrachloride to remove spots of grease. The symptoms caused were smarting around the eyes and mouth, headache, nausea, vomiting, diarrhoea, with acute nephritis in one case and jaundice with liver enlargement in two. All the patients recovered, the two with subacute necrosis of the liver remaining jaundiced for two months.

Exposure in confined spaces

Dudley (1935) described two exposures to the vapour of carbon tetrachloride sprayed from fire extinguishers in confined spaces in British warships and one exposure in a large well ventilated workshop. Four men were poisoned in the first two exposures and were kept under observation in hospital. They all showed impairment of renal function but they all recovered. One suffered from oliguria and jaundice and ten days after exposure developed uraemic convulsions. The blood urea rose to 302 mgm. per 100 c.c. and the patient was practically moribund when on the thirteenth day polyuria developed and he unexpectedly rallied. Another man had almost complete anuria for ten days, but no jaundice and no other symptoms of uraemia. None of the fourteen men who were exposed in the large workshop developed any untoward symptom or showed any impairment of renal function. Personal idiosyncrasy was striking, since there was no relation between the amount of exposure and the severity of symptoms. This author

emphasized that the accidents he described cannot be used as an argument against the employment of carbon tetrachloride as a fire extinguisher. It must be remembered that the prompt use of this liquid has saved a multitude of people from death by burning or asphyxiation by the poisonous gases which are normally present in smoke fumes; while on the other hand it appears that the victims of poisoning from the vapour of carbon tetrachloride, even those apparently very ill, usually make a perfect recovery.

In treatment of cases acutely poisoned by exposure to the vapour in sufficient quantity to cause anaesthesia, it is important that the patient should not be placed upon the floor of the room where the accident occurred, for the vapour is five times denser than air and therefore accumulates on the floor. Chronic poisoning should be treated by alkaline glucose drinks, together with large doses of calcium lactate up to 15 grams a day. Calcium gluconate may be given by intramuscular injection. The use of sugar and calcium salts is based upon the accidental discovery by Minot (1928) that, though carbon tetrachloride causes a severe intoxication in dogs on a meat diet, the addition of calcium salts to such a diet produces a high degree of tolerance to the drug. The symptoms of poisoning are gastro-intestinal irritation and hyperexcitability followed by depression. There is a retention of guanidine in the blood and a hypoglycaemia. The relief and protection given by calcium salts seem to depend upon their antagonistic effect to the retained guanidine. She found that when calcium salts were administered to poisoned animals the nervous symptoms were relieved and the blood-sugar was restored to normal. However, if the blood-sugar was raised by the administration of glucose the hyperexcitability persisted until calcium salts were given in addition.

Treatment of acute poisoning

Of chronic poisoning

Calcium salts

(3)—Tetrachlorethane

Tetrachlorethane, $\text{CHCl}_2.\text{CHCl}_2$, is a very good solvent for cellulose acetate, which, being non-inflammable, is used for purposes for which cellulose nitrate, or celluloid, is not adapted. Cellulose acetate was the chief constituent of the dope used as a waterproof coating for the wings of aeroplanes in the War, and it is now used to make non-inflammable cinema film. In 1911 Lehmann proved that tetrachlorethane was the most dangerous of all the chlorinated hydrocarbons, being about four times as toxic as chloroform and nine times as toxic as carbon tetrachloride.

Use as solvent

Toxicity

In 1914 Jungfer reported the first cases of industrial poisoning from tetrachlorethane. They occurred in Germany in an aeroplane plant where eight men were employed spraying a solution of cellulose acetate over the linen which covered the wings. Four of the men became jaundiced, and one died. This incident saved the Germans from serious trouble in aeroplane manufacture, for before the outbreak of war the use of this solvent in aeroplane doping was prohibited.

Jaundice

In England the first cases came to light in November, 1914, when nineteen workers developed jaundice in an aeroplane works at Hendon.

*Exhaust
ventilation*

One man died after working eleven weeks as a doper, and it was proved that his death was due to tetrachlorethane (Willcox, 1915). The large number affected at the same time was due to the fact that a plenum system of ventilation was installed in the works and it blew the heavy vapour into every corner of the large shed where the work was being done. Aeroplane works were springing up all over the country, overtime was being worked to the utmost, and all the dope used contained the noxious ingredient. Periodic medical examination at fortnightly intervals in the 50 or 60 factories was organized. Exhaust ventilation by fans which changed the air in the doping rooms 25 to 30 times an hour was insisted on, and alternation of employment was recommended. Conditions were ameliorated to such an extent that no outbreak affecting so large a number of workers in any factory occurred subsequently, but there were many isolated cases and deaths, and many workers continued to be suspended at the medical examinations. Attempts to solve the problem by diminishing the quantity of tetrachlorethane in the dope failed, for even as little as 10 per cent proved to be dangerous. Pressure was brought to bear to find a substitute for tetrachlorethane and in July, 1917, the War Office and Admiralty were able to announce that no dope containing tetrachlorethane was being made or used. Seventy known cases of toxic jaundice with twelve deaths had been reported up to that time (Legge, 1917).

*General
symptoms*

The symptoms of poisoning are a general malaise, loss of appetite, nausea, headache, and constipation. After indefinite symptoms of this kind lasting several days or even weeks jaundice develops, and vomiting is then likely to become more marked. In fatal cases necrosis of the liver is found in the form of acute red and yellow atrophy. In one case the liver weighed only 19 oz. Minot and Smith (1921) found that the blood changes in mild poisoning consist of an increase of large mononuclear cells up to 40 per cent, with a slight elevation of the white count. Parmenter (1921) used the above test in order to detect early poisoning among the workers in a silk factory, and claims that he prevented in this way the development of a single case of jaundice. Amyl acetate can often be used as a solvent in place of tetrachlorethane.

*Necrosis of
liver**Blood count*

(4)—Trichlorethylene

*Industrial
uses*

The purveyors of trichlorethylene, $\text{CHCl}:\text{CCl}_2$, recommend it as an ideal non-inflammable non-poisonous solvent, but experience shows that it is far from harmless. It is used extensively in dry cleaning and it has assumed an important place in the list of fat and rubber solvents displacing to some extent carbon tetrachloride. Stüber (1931) recorded no less than 284 cases of poisoning from trichlorethylene, including twenty-six deaths, in German industry; she described the powerful narcotic effect of trichlorethylene, loss of consciousness having occurred in 117 cases. Twelve of the deaths occurred in men who failed to recover consciousness after prolonged exposure to a large dose. Chronic

exposure has been held responsible for paralysis of the sensory fibres of the fifth nerve, and also for retrobulbar neuritis followed by optic atrophy. An indirect form of injury to the eye has been noted by the German factory inspectors who have found corneal ulcer resulting from a foreign body in the eye, the workman not having been aware of its presence because the cornea had been rendered insensitive. *Corneal ulcer*

Apparently trichlorethylene is not so likely to attack the liver as tetrachlorethane. Willcox (1934) described a case of toxic jaundice in a boy aged 16 years who had been employed dipping safety razor blades into a tub containing trichlorethylene. Before admission to hospital he had been jaundiced for a month and had frequently vomited. The temperature was normal and the liver enlarged. There was a little albumin in the urine. Gradually the jaundice cleared up and the liver became normal in size. *Jaundice*

When solutions containing trichlorethylene are applied to the interior of closed vats the men should work in pairs, relieving each other frequently. The man in the enclosed space should be provided with a life-belt and also with an apparatus through which he can breathe air from outside. The use of capsules of trichlorethylene for trigeminal neuralgia is inadvisable. After its introduction about 1925 this mode of therapy remained popular for some time but eventually proved disappointing. *Precautions*
Therapeutic use in neuralgia

12.—OTHER ORGANIC COMPOUNDS

(1)—Carbon Disulphide

1538.] Carbon disulphide (CS_2) is a colourless liquid becoming yellow on standing under the influence of light, with an ethereal odour when pure but a very unpleasant smell if impure. It has an extremely low auto-ignition temperature so that even contact with a warm steam pipe or electric lamp bulb may be sufficient to cause ignition of the vapour. The minimal explosive mixture in air is 19 volumes in 1,000. Carbon disulphide is used in the rubber industry, in the manufacture of artificial silk, in extraction processes, in pharmaceutical processes, in the manufacture of waterproof cements and transparent paper, in the perfume industry, in the manufacture of matches, and as an insecticide for vines and tobacco plants. *Industrial uses*

Late in the nineteenth century cases of poisoning in which mental symptoms predominated were described (Laudenheimer, 1899). About this time factories were known in which the windows of the vulcanizing room had been barred to keep men in an acute stage of poisoning from leaping out during attacks of mania. *History*

Inhalation of concentrated vapours of carbon disulphide causes a narcotic condition preceded or followed by delirium and accompanied by dilatation of the pupils, loss of reflexes, and in severe cases respiratory paralysis and death. Slighter cases are characterized by headache, *Acute poisoning*

giddiness, breathlessness, vomiting, precordial and abdominal pain, and palpitations. The symptoms may subside rapidly on removal of the patient to the fresh air or some may persist for several weeks or even months after an acute attack.

Chronic poisoning

The symptoms of chronic poisoning have been classed as psychopathic, Parkinsonian, polyneuritic, or gastro-intestinal. Mild chronic poisoning is characterized by fatigue, giddiness, heaviness and pain in the limbs, increasing pain in the forehead and temples, restlessness, and difficulty in concentration accompanied by tingling in the legs. The psychosis which sometimes occurs is most commonly of the maniacal type with acute confusion, delirium, and hallucinations. The disorder may subside after a few months or may pass into incurable dementia (Peterson, 1892). In persons disposed to hysteria carbon disulphide may act as an exciting agent (Pierre Marie, 1888). A number of cases are characterized by the tremor, muscular hypertonicity, ataxy, and mental depression of the Parkinsonian syndrome (Quarelli, 1930). In a typical case weakness of the limbs, irritability, and seborrhoeic facies are seen. The most noticeable physical sign is tremor suggesting paralysis agitans affecting arms, hands, tongue, face, and eyelids. In the polyneuritic syndrome there is loss of power in the muscles of the upper and lower limbs so that the gait is unsteady and the grip weak. Loss of sensation is less constant than loss of motor power, but in severe cases anaesthesia has been present from the chin downwards. Diminution of visual acuity progressing to amblyopia occurs in a few cases. It may be due to retrobulbar neuritis and a bilateral central scotoma for colours has been recorded. Nausea, vomiting, abdominal pain, and constipation are common early symptoms of chronic poisoning. Anaemia with a low colour index is sometimes seen but is rarely severe. Impotence has been recorded.

Retrobulbar neuritis

Preventive treatment

The manufacture, handling, and use of carbon disulphide should be carried out as far as possible in air-tight closed automatic apparatus. Ventilation of the work-rooms should be by downward exhaust ventilation at floor level. Workers should stand on platforms and not work in pits. Substitutes for carbon disulphide with less toxic properties should be adopted whenever practicable, as for example carbon tetrachloride, trichlorethylene, and acetone, according to the precise process in question. Alternation of employment with rest periods, or work in shifts should be arranged. Waterproof clothes, gloves, and footwear are necessary, but clothes, walls, and floors readily become impregnated and require to be frequently and thoroughly cleaned. Regular medical examination is called for, and every workman showing tremor of the hands, weakness of the legs, or a visual defect should be transferred at once to other work or rejected altogether. Susceptibility may manifest itself afresh, even after prolonged treatment, as soon as further exposure takes place. Susceptible persons should not be employed. Special precautions should be taken against the risk of explosion and fire.

(2)—Acetone

Acetone, $\text{CH}_3\text{CO}\cdot\text{CH}_3$, is an excellent solvent for cellulose acetate and nitrocellulose; it is used in making celluloid, artificial silk, and cordite. No cases of chronic poisoning from acetone have ever been reported. If inhaled in excess it has a stupefying effect like that of alcohol but nothing worse.

*Industrial uses**Mild acute effects***(3)—Diethylene Dioxide**

Under the trade name dioxan, diethylene dioxide, ($\text{C}_4\text{H}_8\text{O}_2$), is used as a degreaser, as a solvent for nitrocellulose coatings, in the manufacture of artificial silk, and in the preparation of paint removers. According to Yant *et al.* (1930) acute poisoning from the vapour consists in irritation of eyes, nose, throat, and bronchi with narcosis if the concentration is high.

Industrial uses

In 1934 Barber recorded the deaths of five men which occurred from exposure to dioxan in the manufacture of artificial silk in a works near Derby. The process on which they were employed had been in use for a considerable time, but for four or five weeks before they became ill exposure to the vapour was intensified by the speeding up of work on one machine. All the men who died worked on this machine. Diethylene dioxide is not highly volatile under ordinary conditions, but here the men in the course of their duties had to put their heads into the vat containing the noxious substance.

Artificial silk

The premonitory symptoms were nausea, vomiting, and abdominal pain. In two cases an abdominal emergency was diagnosed. In no case was there jaundice to indicate necrosis of the liver. From about the third day of the illness the urine was scanty, and in one case it was found to contain blood and albumin. The symptoms of uraemia with suppression of urine were predominant after the first few days and death occurred in about a week. In one case the blood urea reached 346 mgm. per 100 c.c. The blood count in three cases showed no anaemia nor change in the red cells, but a leucocytosis (24,000 leucocytes per c.mm.) with a high percentage of neutrophils was found. In the four cases submitted to necropsy haemorrhagic nephritis was found, associated with areas of necrosis of the liver without bile staining or fatty change. Absorption evidently occurred by inhalation and the severity of the changes in the kidneys suggests that death was due to the great increase of the dose which occurred when the process was intensified.

*General symptoms**Urinary symptoms**Blood picture**Morbid anatomy***13.—INJURIES FROM X-RAYS**

1539.] Within three months of the announcement by Röntgen of his discovery of X-rays in November 1895 it became known that conjunctivitis could occur after some hours of exposure to irradiation. Within a year erythema, swelling and necrosis of the skin, alopecia,

*X-ray
pioneers*

and chronic radio-dermatitis were reported. In 1897 attention was directed to the acute constitutional symptoms, namely, colicky abdominal pain and diarrhoea. By 1902 Codman was able to collect 171 cases of accidental X-ray burns, less than half of which were serious and about one-third of which occurred in X-ray workers. More than two-thirds of these injuries occurred in the first two years of the use of X-rays. In 1902 a case of cancer was recorded following chronic ulceration caused by X-rays. By 1911 Hesse collected 94 such cases, of which 54 occurred in medical men or technicians, and in 1914 Feygin tabulated 104 cases of malignant disease caused by X-irradiation.

First death

The first death recognized as due to the action of X-rays occurred as recently as 1914 in a radiologist, Tiraboschi of Bergamo.

He had worked for 14 years with X-rays and had taken no precautions. For several years he had had a radio-dermatitis of the left hand and of the right side of the face. In the last three years of his life he lost his strength and became pale. Finally he bled from the gums and necropsy revealed aplastic anaemia together with atrophy of the testes (Faber, 1923).

In 1922 Ledoux-Lebard estimated that 100 radiologists had died from malignant disease due to their occupation.

*Professional
workers*

Deaths occurred among radiologists exposed to X-rays before the importance of adequate protection was realized and unfortunately still occur. So far nearly all the victims have been research workers, radiologists, laboratory assistants, technicians, and nurses.

*Industrial
workers*

Cases of industrial origin did not occur until later, because the use of X-rays in industry began later. Industrial workers, unlike professional workers, are often quite ignorant of the possible dangers of the apparatus they use, so that industry is now, with respect to the use of radio-active substances, about where medical practice was in 1914. There is, however, no reason why the lamentable history of the pioneers in the medical field should be repeated. The human experiments have been made, the tragic results of carelessness demonstrated, and the measures necessary for adequate protection are known and available to anyone who cares to learn them.

*Industrial
uses of X-rays*

The possible uses of X-rays in industry are many and varied, but apparently little developed as yet. They may be used for the detection of defects, cracks, and blowholes in castings, of defects in alloys from faulty mixture, of corrosion in cables or gas cylinders, and of defects in reinforced concrete or in welding. Rubber heels may be examined by the fluoroscope to see if the metal plate is in the centre. X-rays are also used to sort fresh eggs from stale, to reveal mineral adulterants in vegetable foods, and weevils in grain. For the examination of metals and all thick specimens very penetrating rays must be used.

Clinical picture

Injuries which follow a short single exposure, or perhaps several exposures, may vary enormously in intensity. In mild cases there is

simply a transient reddening, lasting a few days and followed by scaling and loss of hair. If the burn is deeper, blisters appear which may be serous or purulent, and the condition resembles that following a scald but is less acute and slower to heal. Sometimes the process, instead of disappearing in a few weeks, penetrates to the deeper layers of the skin and to the subcutaneous tissues with the formation of a leathery slough surrounded by a brawny indurated swelling with ill defined limits. The process is exceedingly slow and obstinate and has a tendency to progress and to resist treatment in a remarkable way. It is at times very painful.

X-ray burns

In chronic X-ray dermatitis the changes in the hands begin round the base of the nails as a peculiar erythema and gradually increase. Transverse and longitudinal ridges appear on the nails, which become brittle, assume a characteristic dirty brown appearance, tend to separate from the matrix, and eventually thicken and form shapeless masses. The skin becomes uniformly red and atrophied; small warts appear, increase in size and number and, when situated over the knuckles, crack and cause much pain. Later the dry thickened skin shows telangiectases, absence of hair, paronychia, and ulcers which are slow to heal and prone to break down. The hair follicles and the sebaceous and sweat glands completely disappear in cases of long standing. The freedom of the palms of the hands may be due to the naturally thicker skin there, but the greater liability to exposure of the backs of the hands and fingers is probably the more important factor. The lesions are as a rule slowly progressive. Post-irradiation telangiectases, which have been regarded as compensatory for obliteration of the vessels in the corium, usually appear within two years, and sometimes in the absence of an initial erythema; in some instances the interval between irradiation and the appearance of telangiectases is prolonged, even to fifteen years. If exposure is continued the lesions may progress to involve the tendon-sheaths and joints. There may be intense pain of which the severity is out of proportion to the size of the lesions; it is caused by the exposure of nerve-endings.

Dermatitis

Warts

Ulcers

Telangiectases

Lesions in tendons and joints
Pain

Squamous-celled carcinoma is almost always the form of malignant disease which has followed excessive X-ray exposure and long continued X-ray dermatitis in man. Although most often seen in radiologists and manufacturers of X-ray apparatus, X-ray carcinoma may also occur in patients who have undergone treatment by X-irradiation. In 1914 Feygin collected six cases of this kind. One of the earliest victims of X-ray carcinoma was a man engaged in the manufacture of X-ray lamps (Friebe, 1902). The interval between the onset of chronic X-ray dermatitis and the appearance of malignant disease varies from three to twenty-seven years. The average of 35 cases was seven years (Feygin). The age incidence from 35 to 50 is comparatively early, that of ordinary carcinoma of the skin being between 55 and 58. The most frequent site of the growth, which is not uncommonly multiple, is on the backs of the hands and fingers, and the hand more exposed appears to be the one more severely affected, the left in radiologists and the

Squamous-celled carcinoma

- right in those engaged in the manufacture of apparatus (Feygin). Among radiologists carcinoma usually develops in an ulcer, less often in keratotic areas. The predominating symptom is pain, which may be constant and very severe and has been ascribed to invasion of the terminations of nerves by the growth and to a neuritis.
- Pain*
- Basal-celled carcinoma* Occasionally basal-celled carcinoma results from X-irradiation. In one case a basal-celled carcinoma of the scalp appeared eighteen years after epilation for ringworm (Burrows). A case has also been recorded of multiple basal-celled carcinomas on the trunk of a radiographer (O'Donovan, 1927).
- Constitutional symptoms* Constitutional symptoms only became prominent after the introduction of deep X-ray therapy, in which massive doses of deep penetrating rays were given.
- In 1923 A. E. Barclay gave the following description of his own symptoms. After 12 years' work and much screen examination with inadequate protection during the War, he began to have painless attacks of profuse diarrhoea, at first without other symptoms but later attended by initial malaise, nausea, vomiting, and on a few occasions by the passage of intestinal casts. Eventually it became necessary for him to give up work and the symptoms then ceased after three weeks. Return to work was followed by an attack 20 days later, and on eight occasions such an interval of 18 to 20 days was definitely established. He then adopted the most efficient means of protection known, a lead apron to cover the abdomen, and remained free from further attacks.
- Severe type* Severe constitutional symptoms may occur. They are nausea, uncontrollable vomiting, sometimes with haematemesis, diarrhoea with the passage of blood, abdominal pain and distension, fever up to 104° F., restlessness, profound prostration, progressive cardiac failure, small rapid pulse, and dyspnoea. When death has occurred it has usually taken place about the fourth day from the onset. Both animal experiments and necropsies of human victims show that the application of X-rays to the abdomen may result in necrosis of the intestinal mucosa.
- Death*
- Sterility* As long ago as 1905 unsuspected sterility was found in eighteen persons who had for various periods been exposed to X-rays (Brown and Osgood). As acute degenerative changes are known to follow vigorous irradiation in almost all the organs of the body, the development of chronic fibrosis should be anticipated as a further result. In two of the famous radiologists who died from X-ray injuries, Tiraboschi and Nordentoft, necropsy revealed fibrous atrophy of the testes (Faber).
- Blood changes* Changes in the blood in X-ray workers were early noted and have been extensively studied. The lymphocytes are first increased in number by small doses of X-rays, then diminished. The red cells may also be increased at first, but anaemia sets in later and may become very extreme. In patients who recover the anaemia is slower to disappear than is the leucopenia. Tiraboschi died of a profound anaemia evidently aplastic in character (Faber, 1923). To-day the possibility of exposure to radium should always be excluded before attributing aplastic anaemia in an X-ray worker to X-irradiation.

Preventive treatment

Methods to protect the X-ray worker from injury have been worked out all too slowly. Within the first few months after their discovery it was found that X-rays were stopped more effectively by lead than by any other common metal. Hence lead for protection came into use very early. To-day lead, lead glass, lead rubber, and lead bakelite are extensively used. Transparent lead glass windows in tube containers were first used about 1900. At that time the need for protecting both operator and patient during radiographic exposure was very great, because low voltages were used with consequent long exposure to a very soft and easily absorbed radiation. For example, to radiograph the spine required exposures up to one hour. That the radiologist was not more frequently affected by the scattered radiation of such exposures was due to the fact that during them he might retire to another room to see other patients. About 1903 there appeared a multitude of protective devices to be worn by the radiologist, including apron, jacket, gloves, and goggles. This type of protection gradually reached its peak about 1914, when necessity threw caution to the winds and the more elaborate devices gave place to means of protection which were built into the apparatus. To-day there is international agreement as to the most effective methods of prevention. In Great Britain such methods have been widely adopted and, although they have no strictly legal recognition, powers of inspection and approval have been placed in the hands of the National Physical Laboratory.

*Protection by lead**Built-in protection*

It is important that the industrial physician should plan measures for the protection of employees against the dangers of X-irradiation, for in large manufacturing establishments there are X-ray departments for diagnosis as extensive and as much used as the average hospital department. Here the problem may include protection of workers in neighbouring rooms, for unless walls and floors are very thick or are rendered impermeable by the use of lead, X-rays may pass through them and cause injury.

*Protection in industry**Symptomatic treatment*

X-ray carcinoma should be treated by radium or by diathermic coagulation. H. Bordier, a victim of the disease, claimed that radium aggravates the dermatitis, as occurred in the case of his teacher J. Bergonié of Bordeaux. Bordier strongly recommended diathermic coagulation under a local anaesthetic and J. Nicholas, who was himself treated in this way, confirmed the benefit obtained by this method. Aplastic anaemia should be treated by repeated blood transfusions.

14.—INJURIES FROM RADIO-ACTIVE SUBSTANCES

1540.] Considering the much larger number of workers in X-rays than in radium, the *gamma* rays of radium appear to have a greater tendency

*Effect on
bone marrow*

than X-rays to cause aplastic anaemia; this impression is supported by the experimental evidence that the penetrative *gamma* rays of radium reach the bone marrow more readily than do X-rays (Moltram). Examination of the workers in the London Radium Institute where radium applicators are prepared and tested, and also of hospital attendants who apply them, revealed a low white-cell count in more than half the cases examined (Moltram and Clarke). In the workers definitely exposed to radium the red-cell count was low as compared with employees not so exposed. Three fatal cases of aplastic anaemia occurred in this Institute, one in a nurse and two in laboratory assistants. Weil and Lacassagne reported the cases of two chemical engineers working with radium and thorium-X. One of them died of aplastic anaemia and the other, although exposed to the same form of radiation, died of typical myeloid leukaemia. Attractive as it might be to suppose that small doses of X-rays or radium exert a stimulating action on the bone marrow, this idea is speculative, and at present it is safer to be content with the view that the occurrence of leukaemia in workers with radium and X-rays is a coincidence (Rolleston).

*Aplastic
anaemia**Luminous
paints*

The chief use of radium salts in industry has been in the manufacture of luminous paint for the figures of clocks and watches and certain important parts of the machinery of aeroplanes. There is an interesting but rare form of industrial risk from the swallowing of radio-active substances in this work. This has occurred at two factories only, one in New Jersey and the other in Connecticut (Flinn). Twenty deaths have occurred, 16 of girls employed in painting luminous dials and 4 of chemists or physicists. In the New Jersey works 48 cases, of which 18 were fatal, occurred among some 800 workers who were employed there from 1917 to 1924.

*Radium
pioneers*

Dermatitis due to radium, isolated by the Curies in 1898, was reported in October 1900. In December of the same year Giesel published an account of the skin lesion caused by exposing his arm for two hours to a celluloid capsule containing radium bromide. In the following year Becquerel, the discoverer of radio-activity, and P. Curie described their own experiences; Becquerel had carried an insufficiently protected tube of radium salts in his waistcoat pocket for six hours; after a week the skin became red and eleven days later it ulcerated. Curie repeated Giesel's experiment, keeping radium chloride in contact with his skin for ten hours, and in three weeks' time an ulcer appeared. Dermatitis has since been reported in a number of persons engaged in making radium preparations and less often in medical men.

*Watch
industry*

In the New Jersey watch industry most of the cases occurred from four to seven years after the girls had left the works. The ill effects included severe anaemia, sometimes aplastic, necrosis of the jaw, spontaneous fractures, and sarcoma of bone. The results of an inquiry into this occupation in the United States were summarized by Martland (1931). The paint consisted of crystalline phosphorescent zinc sulphide rendered permanently luminous by the addition of a very small propor-

tion of insoluble sulphates of radium, mesothorium, and radiothorium. The girls affected introduced the paint into their mouths through the habit of pointing the brush between their lips, and swallowed it for periods of from one to four or more years. The insoluble radio-active materials became deposited in the body to such an extent that even during life radio-active emanations could be detected in the expired air. After death the bones were found to be the tissue in which the materials had mainly accumulated. The anaemia resulted from the continuous bombardment of the haematogenous marrow by *alpha* particles and it was found that these changes were quite different from those due to external irradiation with *beta* and *gamma* rays only. The necrosis of the jaw was similar to that produced by phosphorus and is attributed to infection supervening upon changes in the bones.

*Ingestion of
mesothorium*

*Deposition in
body*

*Necrosis of
jaw*

Radio-activity in the bones and teeth could be demonstrated by autophotography. Dental films in dark paper envelopes when strapped to the bones showed photographic impressions in from fourteen to thirty days. The outlines of metal clips and coins placed between the bone and the surface of the film were clearly visible. These autophotographs were produced by *beta* and *gamma* rays coming from deposits in the bones, the *alpha* rays being screened and filtered out by the paper covering the dental film. The bones when placed directly on photographic plates or films produced photographic impressions in as short a period as three days. After seven days' exposure the irregular distribution of the radio-active deposits could be plainly ascertained. Bones incinerated to a white ash and given thirty days in which to regain their equilibrium, when placed on photographic films produced photographic impressions in from two to three days' exposure (Martland and Humphries).

*Auto-
photography*

*Deposits in
bones*

Dr. S. A. von Sochocky, research chemist and technical director of the company in which the New Jersey cases occurred, died of aplastic anaemia in 1928 (Martland, 1929). The luminous paint used by the girls in the factory was made according to a formula which he had worked out. From 1913 to 1921 he personally extracted about 30 grams of radium from the ore and was exposed continually to heavy penetrative radiation. He was also exposed to the inhalation of radio-active dust in the crystallizing laboratory and on four occasions to explosions of tubes containing high concentrations of radium and mesothorium. He had an extensive radium dermatitis of the fingers of both hands and later developed necrosis of the jaw with buccal lesions. In 1925 he devised methods for measuring the amounts of radio-activity in the bones at necropsy. At this time he tested his own expired air and found larger amounts of emanation than in any of the factory girls examined. He thus realized the hopelessness of his own condition but was stoical to the end. He was in a fair state of health and able to do his work until August, 1928, when he became weak, pale, and dyspnoeic. Blood examination showed red cells 1,720,000 per c.mm., haemoglobin 28 per cent, white cells 4,000 per c.mm., with polymorphonuclears 48 per cent. Later the white-cell count dropped below 2,000 with scarcely any granular cells. The blood platelets dropped to less than 40,000 per c.mm. Ultimately he was kept alive by 13 blood transfusions varying from 450 to 900 c.c. and given every fourth day. Except for a fine purpuric eruption over the extremities, which

*Radio-active
dusts*

*Aplastic
anaemia*

appeared in crops, there was no bleeding until the last. He died a horrible death, with haemoptysis, haematuria, retinal haemorrhages, and terminal broncho-pneumonia. Necropsy showed radio-active deposits in the lungs, the portal of entry evidently having been the respiratory tract.

*Radiation
osteitis*

*Sarcoma of
bone*

*Alpha
particle as
new
carcinogenic
agent*

Lethal dose

*Preventive
treatment*

*Destructive
capacity
of alpha
particles*

*Factory
supervision*

In certain cases anaemia and necrosis of the jaw did not occur, but after a number of years generalized changes in the bones developed with deformities and sometimes spontaneous fracture, a condition known as radiation osteitis. In addition to the seventeen deaths from intractable anaemia and two from necrosis of the jaw, one girl died in 1924 from a sarcoma of the femur and another girl in 1927 from a sarcoma of the scapula. The painting of dials was prohibited in 1924. Since no further cases of anaemia had appeared by 1929, there seemed reason to hope that the danger was over; but in the following two years three more deaths occurred from the same cause. Altogether, therefore, there have been twenty cases of death from occupational mesothorium and radium poisoning, of which five were due to a bone sarcoma.

It is interesting that the watch-dial industry has revealed a carcinogenic agent hitherto unknown, namely, continuous bombardment by the *alpha* particle. Although this agent is quite different from all other known carcinogenic agents, and although its action is continuous, there is the usual prolonged period before malignancy becomes manifest. The *alpha* particle can be held responsible because more than 92 per cent of the radiation coming from the bones are *alpha* and only 8 per cent *beta* and *gamma*. The total amount of radio-active material in the deposit necessary to produce fatal results is extremely small; 0.01 mgm. distributed over the whole skeleton is sufficient to produce a terrible death years after it has been ingested. Radium is thus the most deadly poison known; tetanus toxin previously held the record with a lethal dose of 0.22 mgm.

The *alpha* particles, consisting of the nuclei of helium atoms, are shot out with great force, travel at a high speed, and possess an enormous momentum on account of their mass which is much greater than that of *beta* rays. They collide with other atoms with powerful impact, which disrupts them and produces molecular chemical changes. Thus *alpha* particles decompose water into hydrogen, oxygen, and hydrogen peroxide, and hydrochloric acid into hydrogen and chlorine, expending locally about 100 times as much energy as *beta* rays and acting in a manner correspondingly more destructive of human tissues.

It is obvious that ingestion or inhalation of radio-active materials in industry is highly dangerous and that all occupations involving the handling of such substances should be strictly controlled and supervised. Outside New Jersey and Connecticut the practice of pointing the brush with the lips is unknown. The International Labour Office found by inquiry from watch factories in Switzerland, France, Germany, Austria, Great Britain, and Belgium that the painting in those countries is done with a stylet which is not sucked, and that no ill-effects have been observed. In Great Britain the number of workers in this trade

in 1925 was less than ten. The paint contained 0.0375 mgm. of radium bromide per gram of zinc sulphide. Out of seven British women engaged in luminous painting for periods of one to ten years, two showed a relative diminution in the number of polymorphonuclear leucocytes and one showed leucopenia with 21 per cent of polymorphonuclear leucocytes (Legge).

Though medical practice is now almost safe so far as X-irradiation is concerned, matters are very different in the case of radium. There is no doubt that many people are affected by handling radium, chiefly by the *gamma* rays. Their penetrating power is so great that it is not practicable to protect completely those who handle radium. The British X-ray and Radium Protection Committee have had investigations made in the radium centres throughout Great Britain from 1930 onwards, and not uncommonly one or more of the radium personnel shows signs of too much radiation. In the case of those who carry radium about, the weight of lead they can bear to carry only partly protects them. The surgeon handling radium also is ill-protected. In the case of a man using 120 mgm. of radium for treatment of carcinoma of the cervix uteri, protection is very difficult as each time he has to handle radium closely and carefully (Russ). Surgeons

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TOXICOMANIA

See DRUG ADDICTION, Vol. IV, p. 246

TRACHEA DISEASES

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Reference may also be made to the following titles:

DIPHTHERIA	GOITRE AND OTHER DIS-
ENDOSCOPY OF THE UPPER	EASES OF THE THYROID
RESPIRATORY AND ALI-	GLAND
MENTARY TRACTS	MEDIASTINUM DISEASES
	OESOPHAGUS DISEASES

1.—ABNORMALITIES

*Congenital
abnormalities*

1541.] Congenital abnormalities of the trachea are rare, but the form associated with congenital atresia of the oesophagus, in which the upper part of the oesophagus forms a blind pouch, is of some clinical importance (see Fig. 6). The lower portion narrows as it ascends from the cardiac end of the stomach and terminates superiorly by opening into the posterior aspect of the trachea above the bifurcation (see also OESOPHAGUS DISEASES, Vol. IX, p. 291). The infant has great difficulty in swallowing and milk is regurgitated with coughing and retching; he becomes dyspnoeic and cyanosed and death occurs in a few days. A method of surgical management of these patients has been described by Leven (1936).

Tracheocele, sometimes known as arocele or hernia of the trachea, *Tracheocele* consists in weakness in the wall of the tube through which its mucosa bulges. The protrusion may give rise to a cyst-like swelling in the neck, which is resonant on percussion. It is often possible to reduce temporarily the tracheocele by pressure.

The trachea can often be palpated in the middle line just above the suprasternal notch and its deviation to one or other side recognized by the loss of the usual sense of resistance in the middle line; but radiology is of far greater value in demonstrating alterations in its position throughout its whole length (see Plates IV and V). In the normal radiograph the trachea is seen as a clear stripe extending from the level of the cricoid cartilage to its bifurcation opposite the body of the fifth or sixth dorsal vertebra. After injection of lipiodol a very clear picture of the trachea is obtained. The trachea, like the apex beat, is displaced towards the affected side in collapse and fibrosis of the lung and away from the side of the lesion in pneumothorax and pleural effusions. Its most marked deformity is kinking or curvature towards an apex of a lung contracted and fibrosed from a tuberculous lesion (see Plate V, A). In severe scoliosis the trachea is deviated towards the side which corresponds to the concavity of the spine. Other types of alteration in the position and shape of the trachea, due to pressure on its walls, are dealt with on page 207.

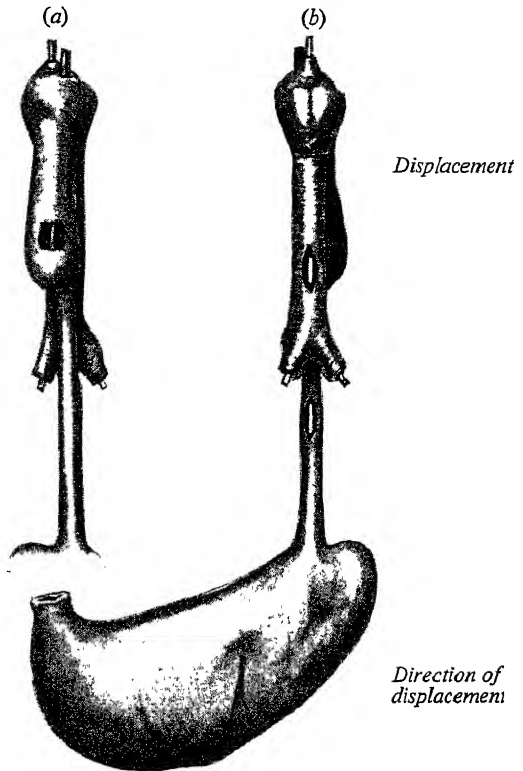


FIG. 6.—Congenital atresia of oesophagus with tracheo-oesophageal fistula. (a) Upper part of oesophagus is of normal width superiorly but slightly dilated at lower end where it ends blindly at level of tracheo-oesophageal fistula. (b) Lower portion of oesophagus communicates with trachea by an opening situated above the bifurcation. A glass rod can be seen passed from the trachea into the oesophagus through the tracheo-oesophageal fistula. (This and Fig. 7 from specimens in the Museum of the Royal College of Surgeons of England, London)

2.—INFLAMMATION

(1)—Acute Tracheitis

1542.] The trachea is often involved in infections of the larynx and bronchi but the resulting tracheitis may remain undiagnosed, being

masked by the more obtrusive laryngeal or bronchial symptoms. Occasionally, however, the trachea may be the primary seat of the affection or may suffer the main brunt of the attack, as in influenza and mustard-gas poisoning.

*Diseases
causing acute
tracheitis*

Any virus or organism capable of producing catarrhal conditions of the upper respiratory tract may cause acute tracheitis. In influenza inflammation of the trachea often gives rise to an intense hyperaemia—the so-called ‘pink trachea’. In diphtheria the trachea may be involved with the larynx and failure of intubation or tracheotomy to relieve difficulty in breathing is often due to membrane in the trachea. Chicken-pox and smallpox may be complicated by acute tracheitis, and in anthrax inflamed and oedematous patches may be present in the lower part of the trachea and large bronchi. In enteric fever small ulcers have been found in the trachea, and in measles it shares in the general catarrhal condition of the respiratory passages. It has been suggested that in whooping-cough the infection starts in the trachea and that the whoop is due to a secondary enlargement of the tracheal glands.

Poison gases

Tracheitis due to gas poisoning has become a subject of importance since the war 1914–18. The trachea may be involved in chlorine and phosgene poisoning, but the most marked effects are found in mustard-gas poisoning (see also Vol. V, p. 507). The tracheal mucosa shows the most severe inflammation, and necrosis of the superficial layers results in the formation of a yellowish-grey slough. On separation of this false membrane the wall of the trachea is left red and glistening. The infected debris tends to accumulate in the finer bronchial tubes, leading to septic broncho-pneumonia or localized abscesses.

*Symptoms:
cough*

The cough has typical manifestations; it is non-productive, hacking, and somewhat metallic; irritating and distressing to the patient, it tends to be paroxysmal and worse after going to bed and during the night. It is often relieved by taking food and especially by a hot drink.

Pain

Acute tracheitis is accompanied by rawness, tightness, or discomfort, sometimes amounting to pain, in the lower part of the neck and behind the upper part of the sternum. This retrosternal discomfort is aggravated by coughing.

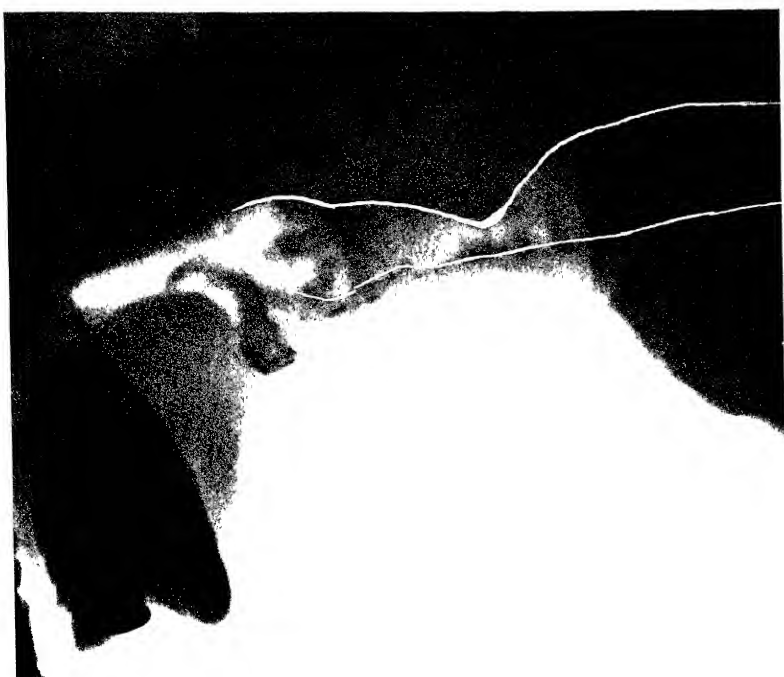
Absence of abnormal clinical signs suggests tracheitis. In uncomplicated tracheitis the voice is unaffected, and on auscultation of the chest rhonchi and other adventitious sounds are absent.

At first there is no sputum but on the second or third day the cough becomes softer and some mucus is expectorated, which in intense inflammation, as in influenza and gas poisoning, may be streaked with blood. Later the sputum becomes muco-purulent. For days or weeks the trachea may remain irritable and paroxysms of coughing, on retiring to bed and on rising in the morning, persist.

In the early stages the chief indications are to allay the distressing and non-productive cough and the painful rawness in the chest. The patient should be kept in bed for a few days and smoking prohibited;



A

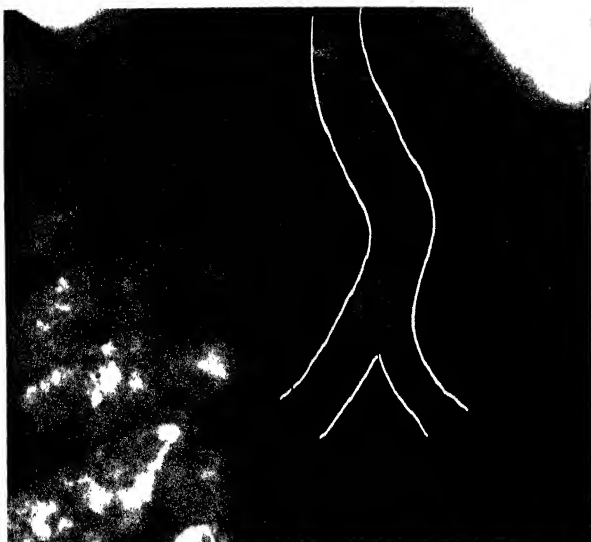


B

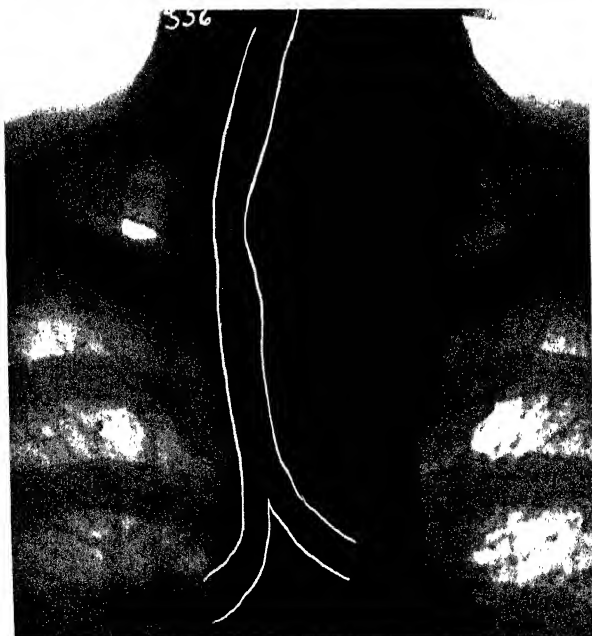
A. Lateral radiograph showing trachea displaced forward by abscess associated with necrosis of the fifth, sixth, and seventh cervical vertebrae.
 B. Lateral radiograph showing secondary malignant deposit pressing on the trachea from behind. A primary tumour had been excised from the thyroid two years previously. The mass ultimately ulcerated into the trachea with haemorrhage. (Radiographs kindly lent by Dr. J. E. A. Lynham)

PLATE IV

}



A



B

A. Radiograph showing fibroid (tuberculosis of left lung with trachea displaced to left. B. Radiograph of case of substernal thyroid with trachea displaced to right. (Radiographs kindly lent by Dr. J. E. A. Lynham)

PLATE V

[To face p. 203

substernal pain can be relieved by counter-irritation with turpentine liniment, mustard plasters, and linseed or other poultices. Inhalation of the vapour of a teaspoonful of compound tincture of benzoin, or 5 minims of oil of pine in a pint of hot water is often soothing. The use of a powder containing codeine phosphate $\frac{1}{4}$ grain, acetylsalicylic acid 5 grains, phenacetin 3 grains, caffeine $\frac{1}{2}$ grain is helpful, and non-productive cough may be soothed by a teaspoonful of Gee's linctus: camphorated tincture of opium, oxymel of squill, and syrup of tolu, equal parts—taken when required.

(2)—Acute Laryngo-Tracheitis

Considerable attention has been paid in American literature to an acute laryngo-tracheitis in infants and children, an infection of the upper respiratory tract occurring in epidemic form, due to streptococci of the haemolytic and *viridans* types and often, in fatal cases, associated with the *Staphylococcus aureus*. Intense congestion and oedema of the glottis and trachea are present. The morbid changes chiefly involve the subglottic region where the loose areolar tissue allows swelling to occur with obstruction of the airway. The prominent symptoms are air hunger, restlessness, and retraction of the ribs, and the condition may be easily mistaken for laryngeal diphtheria. In early cases palliative treatment, as for acute laryngitis and tracheitis, may be tried but if retraction appears tracheotomy must not be delayed.

Bacteriology

Morbid
anatomyClinical
picture

(3)—Chronic Tracheitis

Acute tracheitis may pass into a chronic stage, or the trachea may share in a chronic infection of the pharynx, larynx, or bronchi. This is probably more apt to occur in cigarette smokers. Chronic tracheitis is sometimes associated with chronic hypertrophy of the tonsils and with adenoids. The crusting of atrophic rhinitis may extend not only to the larynx but far down the trachea.

Aetiology

Many chronic irritative coughs without physical signs in the chest are due to chronic tracheitis. The sense of discomfort present in the trachea causes a cough with the characteristics already described under the acute form. The expectoration has been described as resembling a 'moss-agate' stone, being grey and slightly opalescent with dark mottling. It is tenacious and tends to be projected forcibly when the throat is cleared. There may be transient fogging of the voice, due to the sputum temporarily clogging the larynx. The crusts of ozaena may be large enough to produce dyspnoea.

Symptoms

Sputum

It is important in persistent cases to exclude tuberculosis, syphilis, and new growths of the trachea by endoscopic examination.

Diagnosis

Smoking should be prohibited, wintering in a warm and dry climate is advisable, and inhalations and vaccine therapy are worth a trial. Attention must be paid to the condition of the nasal sinuses, tonsils, larynx, bronchi, and lungs.

Treatment

3.—INFECTIVE GRANULOMAS

(1)—Syphilis

1543.] The most important syphilitic lesion of the trachea is a gummatous formation which ulcerates and causes stenosis of the air-passages from the resulting cicatricial tissue. The onset is insidious with an irritating cough, discomfort behind the sternum, and expectoration which may be blood-stained. Later signs of stenosis arise such as severe dyspnoea with loud respiratory stridor. Secondary bronchitis, bronchopneumonia, and bronchiectasis may follow.



FIG. 7.—Stenosis of orifice of right bronchus following syphilitic ulceration of the trachea: viewed from posterior aspect; the bronchial glands at the bifurcation are enlarged

In the museum of the Royal College of Surgeons of England there is an instructive specimen (No. 988-1) in which the orifice of the right bronchus is closely stenosed from cicatrization following syphilitic ulceration low down in the trachea (see Fig. 7). The patient contracted syphilis seven years before the onset of symptoms and for two months had suffered

from dyspnoea on exertion and cyanosis. Such a case shows how a syphilitic lesion can simulate carcinoma of a main bronchus.

Treatment

Treatment should be on ordinary antisyphilitic lines, but considerable stenosis may follow even if the infection is eradicated.

(2)—Tuberculosis

Very few undoubted cases of primary tuberculous disease of the trachea have been reported, but since the introduction of bronchoscopy the common association of tuberculous ulceration of the trachea with pulmonary tuberculosis has been more fully recognized and its incidence placed as high as 40 per cent. Infection is due to contact with infected sputum and is chiefly found in cases of long duration. Laryngeal tuberculosis is often concurrent. The ulceration is wide-spread and the commonest site is along the posterior wall. The symptoms are intractable coughing, dyspnoea, wheezing respiration, and often cyanosis. The prognosis is unfavourable and nearly 50 per cent of those affected die within a year.

Treatment should follow the lines employed in laryngeal and pulmonary tuberculosis. *pulmo- Treatment*

4.-OBSTRUCTION

1544.] Tracheal obstruction may originate from (i) foreign bodies in the lumen; (ii) lesions of the tracheal wall: acute inflammation such as diphtheria and acute laryngo-tracheitis of children; cicatrization after healing of a syphilitic gumma or tuberculous ulceration; scar tissue following mustard-gas poisoning; granulation-tissue following wounds of the trachea, tracheotomy, intubation, or foreign body; and tumours, innocent or malignant, arising primarily from the trachea; (iii) compression or invasion of the wall from without: enlargement of the thyroid gland; intrathoracic goitre; hypertrophy or tumours of the thymus; aneurysm of the arch of the aorta or innominate artery; enlarged tracheo-bronchial glands; oesophageal lesions; and retro-pharyngeal or mediastinal abscess. *Causes*

If the obstruction develops slowly a considerable period may elapse before tracheal symptoms are manifested. As the lumen progressively narrows dyspnoea on exertion with a slight inspiratory stridor becomes noticeable. With extreme narrowing distressing dyspnoea occurs and breathing is difficult and laborious and carried out with aid of the accessory muscles of respiration. Inspiration is usually more difficult than expiration; both are prolonged and accompanied by noisy stridor. If, despite the prolonged inspiration, sufficient air does not enter the lungs retraction appears at the root of the neck and lower ribs. In tracheal stenosis the upward and downward movements of the larynx are not marked as they are in laryngeal obstruction (Gerhardt's sign). The attitude of the patient is typical, sitting up and bent forward with the chin sunk towards the chest to avoid stretching and narrowing the trachea. The typical harsh, clanging, and often paroxysmal cough torments the patient, and the constant fear of imminent suffocation adds to the victim's terrible distress. Pulsus paradoxus may be present. The voice is often faint and weak but is not hoarse as in disease of the larynx, unless paralysis of a recurrent laryngeal nerve has occurred. *Symptoms of tracheal obstruction*

Foreign bodies

When a foreign body is drawn into the larynx an immediate attack of choking, coughing, and wheezing takes place and is followed by a period of freedom from symptoms as the body falls into the trachea. The foreign body is usually sufficiently small to pass downwards into one of the main bronchi, most often the right. When it remains in the trachea, three pathognomonic signs have been described (Chevalier Jackson). (i) The 'asthmatoïd wheeze' is a dry sound heard when the bell of the stethoscope is held at the patient's open mouth. It persists after coughing and expectoration and may be the only sign present for a long time. (ii) When the foreign body is movable, as it generally is when in the trachea, coughing often drives it against the subglottic *Gerhardt's sign* *'Asthmatoid wheeze'* *The 'audible slap'*

*The
palpatory
thud*

narrowing and its sudden arrest there produces a slap which can be heard at the patient's open mouth. This slap may be noticed subjectively by the patient. (iii) The 'palpatory thud' is the name given to the sensation which this sudden arrest transmits to the examiner's finger held on Adam's apple.

*Laryngeal
symptoms*

Cough is paroxysmal and may be severe if the foreign body is movable. It may simulate pertussis. The sputum may be streaked with blood.

Laryngeal symptoms may be present, namely hoarseness and croupy cough, dyspnoea, and cyanosis, especially in young children in whom the subglottic tissues are apt to swell or in whom the larynx may have been injured by the passage of the foreign body or by attempts at its removal.

*Course and
prognosis*

If the foreign body does not produce immediate death from asphyxia the prognosis is better than if it lodges in a bronchus. A rough or sharp substance is likely to cause ulceration and sepsis with subsequent cicatrization and stenosis of the trachea, and there is always the danger of sepsis spreading to the lungs causing septic broncho-pneumonia. The prognosis depends largely on the interval before removal.

Diagnosis

In some cases a history of the inhalation of the foreign body is lacking and laryngeal diphtheria may be suspected. Many foreign bodies, such as coins, teeth, buttons, and pins, may be revealed by X-ray examination. Endoscopic examination is required in the case of non-opaque substances.

Treatment

Treatment consists in the rapid removal of the offending substance. The ideal method is extraction by forceps through a bronchoscope, but if specialist services are not available tracheotomy should be carried out, when the foreign body may be coughed out or removed with forceps.

Tumours

Osteomas

*Tracheopathia
osteoplastica*

Primary tumours of the trachea are much less common than those of the larynx or bronchi, and benign forms are less rare than malignant. Of the non-malignant tumours osteomas arising from cartilage are the commonest. These multiple hard gritty tumour masses produce the condition known as tracheopathia osteoplastica which may exist for many years and produce few or no symptoms, but occasionally hoarseness, cough, and dyspnoea call attention to it. Samuel Wilks in 1857 described a case with ossific deposits in the larynx, trachea, and bronchi; the deposits 'were quite smooth except at the bifurcation of the trachea where a rock-like mass growing from the cartilage protruded into the air passage'.

*Other benign
tumours*

Papillomas, fibromas, and intratracheal goitres come next in order of frequency. Tuberculomas have also been described.

*Malignant
tumours*

Of the rare primary malignant tumours adenocarcinoma and squamous-celled carcinoma are the most common. Sarcomas are even rarer. Secondary growths are uncommon, but direct invasion from carcinoma in adjoining structures is comparatively frequent (see Plate IV, B).

The symptoms of new growth of the trachea are (i) harsh clanging *Symptoms* brassy cough ('gander cough') and often blood-stained expectoration; (ii) stridor with prolonged inspiration; expiration is also prolonged but to a less degree; and (iii) gradually increasing dyspnoea with distressing paroxysmal attacks especially at night. Attacks of dyspnoea may be brought on by swallowing. Cyanosis becomes marked and the condition terminates in asphyxia.

If the tumour is malignant the patient's general health suffers. The growth may spread to neighbouring organs, oesophagus, larynx, and lungs. Metastases are generally regional but several cases have been reported with a cutaneous dissemination. The symptoms call attention *Diagnosis* to the upper air-passages and diagnosis is made by endoscopy and *Treatment* biopsy. The treatment of this condition is surgical.

Compression from extrinsic causes

Symptoms of pressure on the trachea are often accompanied by others pointing to involvement of structures closely related to it, e.g. dysphagia from pressure on the oesophagus and engorgement of the jugular veins, and aphonia, paralysis of the diaphragm, or ocular signs from paralysis of the recurrent laryngeal, phrenic, or cervical sympathetic nerves respectively.

Bilateral enlargement of the thyroid may compress the trachea laterally *Enlargement of thyroid gland* and reduce the lumen to a narrow slit, the so-called scabbard trachea. If the goitre is unilateral the trachea is often displaced and curved greatly towards the opposite side. A rapid enlargement of the thyroid gland produced by haemorrhage into it may give rise to the sudden onset of dyspnoea and cyanosis, which tend to be continuous. Sub- *Substernal goitre* sternal goitre not only displaces the trachea backwards but also compresses it on either side (see Plate V, B). The radiograph corresponds to the sabre-shaped trachea found at necropsy. There is a feeling of substernal pressure, and a sense of suffocation and choking when lying down. Respiratory stridor is often brought out by getting the patient to walk up and down stairs.

The compressibility of the trachea varies with age; at the age of five it offers four times as much resistance to pressure as it does at birth. *Hypertrophy of thymus* An enlarged thymus in an infant may flatten the windpipe with stridor and severe dyspnoea as described by Kopp in 1830 and sometimes called thymic or Kopp's asthma. This is most marked in the first few weeks *Kopp's asthma* or months of life and diminishes after the second year. (See THYMUS GLAND DISEASES, p. 35.)

The trachea deviates to the right just above the bifurcation where the *Aneurysm* arch of the aorta crosses its left anterior aspect. Here pulsation can be seen with the bronchoscope and the windpipe may be compressed by an aneurysm of the arch. As the aortic arch passes backwards it lies above the left bronchus. With each pulsation of an aneurysm of the arch the left bronchus may be thrust downwards and so produce *Tracheal tugging* 'tracheal tugging'.

*Enlargement
of tracheo-
bronchial
glands*

Tuberculous tracheo-bronchial glands may be large enough to press on the trachea and occasionally erode and discharge caseous material into its lumen, thus causing the sudden onset of acute respiratory distress, dyspnoea, and cyanosis. Other causes of enlargement of the mediastinal glands are Hodgkin's disease, metastases from malignant disease in an adjacent organ, especially a bronchus, lymphoid leukaemia, lymphosarcoma, and syphilis. Tracheal breathing and pectoriloquy can be heard in the normal individual from the occiput to the seventh cervical spine; if the tracheo-bronchial glands are enlarged these auditory signs can be heard as far as the fifth dorsal spine. This is known as d'Espine's sign or tracheophony.

*D'Espine's
sign*

*Other
oesophageal
conditions*

Carcinoma of the oesophagus is a common cause of tracheal obstruction, and a foreign body impacted in the gullet is liable to produce a compression stenosis. Both these conditions may lead to oesophago-tracheal fistula. Pharyngeal pouches (see Vol. IX, p. 579) and diverticula of the oesophagus (see Vol. IX, p. 292) may give rise to tracheal symptoms.

*Retro-
pharyngeal
abscess*

In all cases of difficulty in breathing and stridor in infants and children the possibility of acute or chronic retro-pharyngeal abscess should be considered (see Plate IV, A). (See also ASPHYXIA IN CHILDREN, Vol. II, p. 176.)

Diagnosis

The diagnosis of the various forms of compression is often evident, as in the thyroid group, but in cases in which the seat of pressure is

Treatment

in the mediastinum diagnosis may be difficult. The treatment is that applicable to the original condition.

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TRACHOMA

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Reference may also be made to the following titles:

CONJUNCTIVA, INJURIES AND DISEASES
CORNEA, INJURIES AND DISEASES
EYELIDS, INJURIES AND DISEASES

1.—DEFINITION

(*Synonyms.* Trachomatous conjunctivitis; granular lids; granular ophthalmia; granular conjunctivitis; Egyptian ophthalmia; and military ophthalmia)

1545.] Trachoma is a chronic specific contagious disease of the conjunctiva in man; it has no tendency to spread to other tissues except to the tarsus and to the cornea. It is characterized by lymphocytic infiltration and by fibrous hyperplasia. It is chronic in nature but may have an acute onset in the absence of bacterial infection.

2.—EPIDEMIOLOGY

Aetiology

The disease is believed to be the result of infection by the *Rickettsia trachomatis*. In suitable cases and with suitably stained epithelial scrapings the virus particles can be detected under high microscopical magnification. These exist as inclusions within superficial cells of the conjunctival epithelium and are known as *Halberstaedter-Prowaczek Körperehen* (corpuscles), so called after their discoverers, and resemble the inclusions found in epithelial cells in other virus diseases.

Incidence and geographical distribution

It is probable that half of the inhabitants of the world have been infected with trachoma, though in a large proportion of cases the disease has attained a natural cure or is quiescent. There is mass-infection in many countries such as Egypt, Palestine, India, China, and Japan, except among the richer classes; it is common in parts of North and South America, Italy, Poland, and Southern Ireland. It is now rare in England but sporadic cases occur even among the upper classes and when no source of infection can be discovered. The risk of infection for an individual living in a trachomatous country is slight provided he observes strict cleanliness and does not live or sleep in the same room as the indigenous inhabitants. Experience, however, has shown that both children and adults who go to live in a trachomatous country become infected occasionally, even though all possible care is taken as regards prophylaxis; this is especially the case when native servants are employed.

Method of spread of infection

Infection is acquired by the transfer of conjunctival secretion from a trachomatous individual with the disease in an active stage into the conjunctival sac of a healthy person. This may be effected by the hands, by a towel or handkerchief, by a pillow, or, when the infective material has passed down the lacrimal passage into the nose, by sneezing. Transmission of contagion by flies probably occurs but is less common than the foregoing means.

Age incidence

Trachoma may be acquired at any age. In countries where there is mass-infection a mother infects her infant before it is weaned.

3.-CLINICAL PICTURE

(1)—Initial Signs

The incubation period varies from four to ten days. Typically the disease begins insidiously, but often it is ushered in by an acute attack of bacterial conjunctivitis. In the former case the disease may be present for a long time and attain a considerable degree of severity before it is recognized; in the latter case it is only recognizable on the subsidence of the acute symptoms. Atypically it begins with acute symptoms, such as pain, lacrimation, and photophobia, in the absence of bacterial infection.

*Incubation
period and
onset*

(2)—Stages

Until the various anatomical changes in the conjunctiva and cornea are appreciated in the order of their development it is impossible to form any lucid idea of the disease. The classification which is now in common use throughout the world is known as MacCallan's stages of trachoma.

There are four stages, depending on the relative prominence of lymphoid follicles or alternatively of subepithelial lymphoid infiltration; bleb-like excrescences which burst on pressure or alternatively papillary hypertrophy; and formation of connective tissue.

In the first stage (Stage I or Tr. I) the disease may manifest itself either by tiny follicles or aggregations of lymphoid cells in the superficial layer of the conjunctiva or by a generalized subepithelial infiltration of similar cells which gives a red and velvety appearance to the conjunctiva. These manifestations may disappear entirely, without leaving any trace.

First stage

The next stage may be either that of complication or that of benign evolution. The stage of complication (Stage II or Tr. II) exhibits either bleb-like excrescences (Tr. II *a*) or a papillary hypertrophy (Tr. II *b*). The stage of benign evolution (Stage III or Tr. III) is characterized by the absorption of the follicles or of the subepithelial infiltration and their replacement by cicatricial tissue.

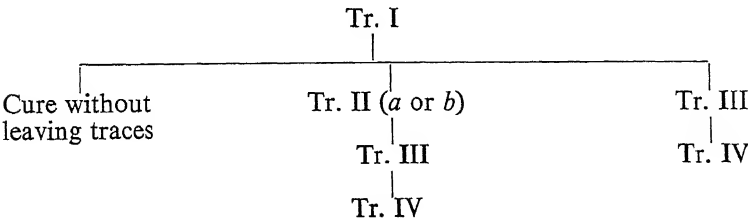
Second stage

Third stage

The last stage (Stage IV or Tr. IV) is reached when follicles or infiltration have been entirely absorbed and replaced by cicatricial tissue. This is the stage of cured trachoma; frequently this stage is never reached.

Fourth stage

The course of the disease may be expressed diagrammatically thus:



With a comparatively small amount of experience cases can be assigned to one or other of these stages. Some cases are on the border-line between two stages and may show, for example, bleb-like excrescences of Tr. II *a* and also a certain amount of cicatrization characteristic of Tr. III; such a case would be noted as Tr. II *a* to Tr. III. For ophthalmologists who practise in trachomatous countries, such as Egypt and Palestine, a more elaborate scheme of classification is required (MacCallan).

(a) Stage I

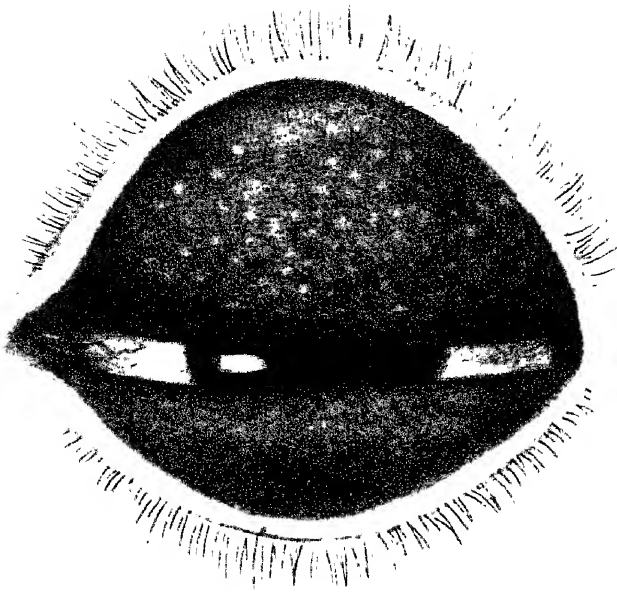
The response to infection by trachoma is a generalized flooding of the subepithelial tissue of the conjunctiva with lymphocytic cells (see Fig. 8). Typically these cells are aggregated into clumps, the so-called



FIG. 8.—Trachoma, stage I: section of conjunctiva showing single follicle with intense subepithelial infiltration with lymphocytes. (From the Author's *Trachoma*)

trachoma follicles; atypically, but not uncommonly, no follicles can be differentiated clinically from the general exudate of lymphocytes. There are therefore the follicular and the general lymphocytic types of onset.

In the follicular type there are, scattered over the conjunctiva of the upper tarsus at the extremities of its upper border, slight roughnesses, forming tiny greyish islets (see Plate VI, A). The rest of the conjunctiva may not show any sign of inflammation, but there is usually a little increase of the conjunctival secretion. The position of early trachoma follicles is considered to be distinctive, but in appearance the isolated trachoma follicle is identical both macroscopically and microscopically



A



B

A. Trachoma, stage I. B. Limbal region in young man, showing trachomatous pannus. $\times 4$. (From the Author's *Trachoma*)

PLATE VI

[To face p. 212

with the follicle of non-trachomatous conjunctivitis. In the general lymphocytic type there is a generalized subepithelial infiltration with lymphocytes which gives the conjunctiva a red, inflamed, and velvety appearance.

General lymphocytic type of Tr. I

In both types of Tr. I characteristic changes occur in the upper fifth of the corneal limbus, where a cellular invasion of the cornea takes place. This cellular invasion appears as an indefinite grey infiltration which often becomes concentrated into a number of tiny grey elevations which do not differ from trachomatous follicles of the conjunctiva in cellular composition.

Invasion of cornea

In response to the irritation caused by this cellular invasion, there is a vascular proliferation; new vessels run centripetally for a little distance towards the centre of the cornea in tissue which is normally devoid of blood-vessels. This new vascularity of the formerly clear cornea together with the grey infiltration constitutes corneal trachoma or pannus and may extend all over the cornea in severe cases and, when such a complication as corneal ulceration occurs, reduce visual acuity to virtual blindness (see Plate VI, B).

Reaction in cornea: pannus

Trachomatous pannus must be distinguished from two other conditions in which the cornea becomes vascularized: (i) the process of healing of a corneal ulcer, and (ii) interstitial keratitis. In trachomatous pannus the vessels spring from the network of marginal loops which can be traced on to the cornea as branches of the conjunctival vessels, i.e. they are superficial. The healing of a corneal ulcer is carried out by vascularization of the edges of the ulcer by the ingrowth of vessels from the conjunctiva; the vessels are fewer and larger than in trachomatous pannus and are localized to the proximity of the ulcer. In interstitial keratitis the vessels cannot be traced from the cornea on to the conjunctiva but disappear at the corneal margin, being derived from the deeply situated vessels of the sclera.

Differential diagnosis of trachomatous pannus

From healing corneal ulcer

From interstitial keratitis

In this stage, as in other stages of trachoma, the disease may be well marked without causing any symptoms of discomfort and the general appearance of the orbital region show nothing abnormal. Symptoms, when present, do not differ from those of any other form of conjunctivitis; there is a slight conjunctival discharge and a sensation as of grit under the lids; the lids may be stuck together in the morning on awaking from sleep.

Symptoms of Stage I

(b) Stage II

This stage exhibits two forms: in the more common, Tr. II *a*, numerous bleb-like excrescences appear on the palpebral conjunctiva of both upper and lower lids; in the less common form, Tr. II *b*, the prevailing feature is a papillary hypertrophy of the conjunctiva.

The numerous bleb-like excrescences which protrude above the surface of the rest of the conjunctiva in Tr. II *a* rupture easily on pressure, allowing their gelatinous contents to extrude. Great care should be taken by the surgeon during the examination of these cases,

Trachoma II a

for if the blebs burst their contents are liable to enter the conjunctival sac of the examiner, resulting in trachomatous infection; the surgeon should therefore always wear protective goggles when examining a case of suspected trachoma. The bleb-like excrescences have the appearance of frog-spawn or cooked grains of sago.

The tarsus is always thickened by an inflammatory exudate, the weight of which causes some drooping of the upper lid, or ptosis. From the thickening of the boat-shaped tarsus there is incurving of the upper lid, and proliferation of the hair follicles follows; the resulting trichiasis (see p. 215) may rub on the cornea, and, if untreated, last for years. The lymphocytic infiltration may spread from the corneal periphery over the whole cornea, with generalized vascularization; being situated between the corneal epithelium and the anterior elastic lamina (Bowman's membrane), it may destroy the latter and, obtaining access to the corneal stroma, cause further permanent opacity.

Trachoma
II b

In the stage Tr. II *b* the trachomatous infiltration or follicular formation is obscured by a papillary hypertrophy of the conjunctiva, giving the appearance of red, raspberry-like processes. This is the result of the throwing up into folds of the superficial epithelium by the intense subepithelial infiltration of lymphocytes.

(c) Stage III

This stage of partial cicatrization or cure may be derived directly from Tr. I, or stages Tr. II *a* or Tr. II *b* may intervene. When it follows Tr. I the reddened conjunctiva is seen to be permeated by a fine network of cicatricial tissue. When following Tr. II *a* the network of cicatricial tissue encloses bleb-like excrescences, which may become squeezed out by the contraction of cicatrization. When affecting Tr. II *b* the network of cicatricial tissue surrounds islands of actively diseased conjunctiva.

Arlt's line

Just inside the inner border of the upper lid there is usually a horizontal white streak of cicatrization called Arlt's line.

A reversion from Tr. III to Tr. II *a* is quite common.

(d) Stage IV

Theoretically this is the final stage, a cure having been effected either naturally or as the result of treatment. The normal epithelium has been replaced by scar-tissue epithelium, and the subepithelial infiltration has been absorbed or replaced by cicatricial tissue.

In many untreated cases this stage is never reached. In all cases invaginations of the diseased epithelium occur, carrying into the depths of the tissue of the lid infecting and irritating material. Thereupon results a remarkable fibrous development, which is characteristic of trachoma and is especially manifested in the pretarsal tissue and in the tarsus. This fibrous development goes beyond the needs of tissue repair.

The implications as regards treatment are obvious. Firstly, the application of drugs to the tarsal conjunctiva cannot be expected to influence invaginated and infected epithelial cells in the deeper tissues; secondly, the expression of the bleb-like excrescences of Stage II *a* removes the contents of many of the superficial follicles and epithelial cysts but can have no effect on the deeper lymphocytic infiltration; thirdly, the employment of chemotherapy cannot be expected to do more than kill the virus, leaving untouched the lymphocytic infiltration and the fibrous hyperplasia.

Other signs of trachoma are as follows: trachomatous rosettes at the limbus, and, after these become cicatrized, Herbert's peripheral pits; trichiasis and entropion, ptosis and narrowing of the palpebral fissure, sinuous lid margin, post-trachomatous degeneration, corneal facets or depressions, superficial punctate keratitis, and epithelial plaques.

4.—SEQUELAE

Pannus is really trachoma of the cornea and an integral part of the disease (see p. 213) and a diagnosis of trachoma should not be made unless it is present. Formerly it was thought to be a sequela which required special operative treatment. *Pannus*

Pannus exists in two forms, one in which the granulation-tissue beneath the epithelium clears up, leaving only the attenuated vessels, and the other in which the anterior elastic lamina (Bowman's membrane), which underlies the corneal epithelium, has been destroyed in places with invasion of the corneal stroma by vascular granulation-tissue. Cicatrization results in permanent opacity, and the abolition of the normal lymph-flow between the corneal corpuscles cuts off their nutrition, thus necessitating the persistence of pannus vessels. All operations for the removal of pannus, such as pannus dissection and peritomy, are absolutely contra-indicated.

Trichiasis, or the condition in which the eye-lashes rub the cornea, is due to the development of supernumerary lashes by offshoots from existing hair follicles. This new development is caused by the hyperaemic condition of the lid margin, which always occurs in serious cases of trachoma. *Trichiasis*

Entropion is an inversion of the lid margin due to cicatricial changes in the tarsus. It may affect one or all four lids. *Entropion*

Ectropion of the lower lid is due to thickening of the tarsus by inflammatory products and subsequent cicatrization. *Ectropion of lower lid*

Apart from the results of corneal ulceration, diminution of the visual acuity results from the trachomatous infiltration of the cornea. While this is active, and careful treatment is applied to the palpebral conjunctiva, great improvement may result, but when cicatrization has occurred improvement cannot be expected. Trachomatous infiltration of the mucous membrane of the lacrimal sac is common in trachomatous *Diminution of visual acuity*
Lacrimal sequelae

countries. Lacrimal probes should not be used in such cases on account of the danger of perforating the sac.

5.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Method of examination

In a suspected case of trachoma both lids must be fully everted. The lower lid may be pulled down by the finger so that the fornix is fully displayed. The upper lid must be everted over a blunt hook in order to examine adequately the whole conjunctiva. It is essential, in order to establish the presence of trachomatous vascularization, to examine the upper periphery of the cornea carefully, under good focal illumination, with a corneal loupe giving a magnification of 8 or 10 diameters. (See EYE EXAMINATION, Vol. V, p. 217.)

Common conditions which may bear a resemblance to trachoma are: follicular conjunctivitis in children, acute conjunctivitis with follicles, and chronic conjunctivitis with corneal vascularization of interstitial keratitis or of former phlyctenular conjunctivitis. Uncommon conditions resembling trachoma are: spring catarrh and swimming-bath conjunctivitis (including blennorrhoea). In none of the above conditions do any of the following pathognomonic signs of trachoma appear: bleb-like excrescences which rupture on pressure with exudation of their gelatinous contents, pannus, punctate depressions at the limbus, i.e. Herbert's peripheral pits, or cicatrization of the upper palpebral conjunctiva.

6.—TREATMENT

(1)—Prophylaxis

In dusty countries where trachoma is rife it is important to wash the face and eyelashes twice a day. The eyelids must not be rubbed with the fingers. Salutation by shaking hands with an infected person and employment of house servants who have any discharge from the eyes are dangerous. If the employment of ayahs or amahs for young children is imperative antiseptic eye-drops, such as zinc sulphate or zinc chloride solution of the strength of 0.5 per cent, should be instilled into their eyes twice a day unless an oculist pronounces them free from trachoma.

(2)—Treatment of Conjunctiva

Stage I

The upper lid is entirely everted on a blunt hook, or better on a MacCallan-Rostovski everter, and the conjunctiva swabbed with 2 per cent solution of silver nitrate. This should be carried out daily or at least five days a week for a month or six weeks. Then drops of a solution of zinc sulphate or zinc chloride 0.5 per cent may be used for a period before recommencing treatment by massage with solution of mercuric chloride 0.25 or 0.5 per cent daily. Silver nitrate must be used carefully to avoid the deposition of silver in the epithelial cells (argyrosis).

Massage with chaulmoogra oil is said by some to have a beneficial effect. Innumerable other remedies including radiotherapy, auto-serotherapy, and high-frequency currents have been advocated; also many secret remedies have been used with disappointment to the patient.

In the presence of the bleb-like excrescences which characterize stage II *a* *Stage II a* surgical interference is essential, namely, rupture of the blebs by expression with Graddy's forceps and scraping with a sharp spoon, after eversion of the lid. For adults local anaesthesia, by the frequent instillation of solution of cocaine hydrochloride 4 per cent and by infiltrating the lids with procaine hydrochloride (novocain) solution 1 per cent, will suffice if care is used. For children a general anaesthetic is required. It is usually necessary to repeat the operation on several occasions before all the blebs towards the fornix and the inner angle of the eye are destroyed. The conjunctiva is then massaged with solution of mercuric chloride 1 in 500 and the eyes are bandaged for an hour only. Subsequently antiseptic drops should be used by the patient until the next operative seance.

In stage II *b* also application of medicaments to the conjunctiva *Stage II b* is useless. Mechanical treatment such as that just described may be employed.

In many cases some bleb-like excrescences still remain. These should *Stage III* be dealt with by mechanical treatment. After some days the conjunctiva may be massaged with solution of copper sulphate 5 per cent or with the old-fashioned copper sulphate stick.

Theoretically treatment is not required in the fourth stage because all *Stage IV* active lesions have undergone cicatrization. There may, however, be areas of the conjunctiva which are not covered by scar-tissue epithelium, and which are susceptible to new infection. It is therefore advisable for all patients with apparently healed trachoma to continue treatment by some such astringent drops as solution of zinc chloride 0.25 or 0.5 per cent.

(3)—Treatment of Sequelae

(a) *Blepharophimosis*

Blepharophimosis is the condition in which the palpebral fissure appears to be contracted at the outer canthus. In many cases of old trachoma it is impossible to evert the upper lid satisfactorily for the purpose of treatment on account of this narrowing of the palpebral fissure. It may be rectified by canthoplasty (for technique of canthoplasty see Vol. V, p. 246).

(b) *Trichiasis and Entropion*

Certain general principles may be formulated as regards operations to rectify trichiasis and entropion: (i) if the conjunctiva requires treatment for active trachoma this should be carried out before operation, except in urgent cases such as corneal ulceration. (ii) The eyelid should

be supported and stretched on a metal spatula or shoe-horn; no form of clamp should be used. (iii) Only in exceptional circumstances should skin be removed from the lid. (iv) Partial operations should never be performed, however tempting it may seem to reduce thereby the extent of the operation.

Operations

Most cases of trichiasis-entropion can be dealt with satisfactorily by one of two operations, which may be performed by any medical man who has already acquired experience in surgical technique. The first is Streatfeild's operation, described by him in 1858, often misnamed Snellen's operation, and depends on the removal of a wedge-shaped strip from the anterior surface of the tarsus. The second, van Millingen's operation, consists in insertion of a graft of mucous membrane into a groove made in the free border of the lid. Many of the operations described in ophthalmic text-books are useless or even dangerous. Streatfeild's operation is described in the article EYELIDS, INJURIES AND DISEASES, Vol. V, p. 248. In a few severe cases, however, the operation as there described does not give quite sufficient results, and then one or two additional procedures may be carried out:

Streatfeild's operation

(i) The entropion spatula is reinserted and a superficial cut 0.5 or 1 mm. deep is made along the whole free border of the lid just posterior to the lashes; owing to the tension exerted by the sutures already inserted the lips of the incision gape somewhat, allowing further eversion of the lash-bearing area. The greatest care must be taken to avoid leaving any hair bulbs in the posterior lip of the wound; if this happens they must be picked out with the point of a knife. (ii) In very severe cases, which are rare except in Eastern countries, the procedure adopted by Cant may be carried out. A vertical incision with stout scissors is made through the whole thickness of the lid at its inner and outer extremities. The incision should extend 3 mm. upwards (for only the upper lid is likely to require this somewhat disfiguring procedure) from the free border of the lid. This allows more complete eversion of the lid margin.

Mucous membrane graft operation

For the mucous membrane graft operation, the metal spatula of shoe-horn shape is inserted under the lid which is made tense thereby. An incision is made along the whole free border of the lid, immediately posterior to the lashes and as close to them as possible, but without injuring them; it should be about 3 mm. deep. The anterior part of the lid—when speaking of operation on the upper lid, for the operation is applicable to either upper or lower lid—which includes all the lashes, is now allowed to slide up towards the eyebrow, to the skin of which it is anchored by a few sutures. Extra effect may be attained by placing a little roll of gauze beneath the sutures. On the posterior part of the lid a horizontal strip of bare tarsus, 3 mm. wide, is thus prepared to receive the graft.

The lower lid is now seized at either extremity with plain dissecting forceps and everted. An injection of procaine hydrochloride (novocain) and adrenaline is made horizontally along the area from which it is intended to remove the strip of membrane. The mucous membrane is gripped with toothed forceps on the right side of the mouth, and with the narrow, blunt-pointed scissors a strip 25 mm. long and 2 mm. broad is cut. This strip of mucous membrane should always be a little shorter and narrower than the bed in the lid margin which has been prepared to receive it; it should be carefully wrapped in a

piece of sterile gauze. The wound in the lid is then sewn up with a blanket suture. The strip of mucous membrane is carefully denuded of submucous tissue and laid on the wound in the lid, without having been in contact with any antiseptic solution. It is carefully pressed into position with the moistened, gloved fingers of the operator, with the raw surface downwards. No sutures are required. A dressing of gauze which has been spread with boric acid ointment is carefully applied and firmly bandaged. This is not removed until the fourth day after the operation, when the skin sutures are removed, as well as the lid sutures. A very light dressing is applied for a few days.

The epilation of misplaced lashes in trachomatous trichiasis should be absolutely forbidden, as after epilation the lashes regrow and are again a danger to the cornea.

Other methods for removal of misplaced lashes

The destruction of hair follicles by diathermy in one second or by electrolysis in thirty seconds may be carried out if there are not more than three misplaced lashes, and if the proper machine is available. I do not consider these procedures to be good practice, as in trachoma these three lashes are, in the majority of cases, the forerunners of numerous other misplaced lashes.

(c) *Ectropion of Lower Lid*

The operative treatment for ectropion of the lower lid (MacCallan's operation) consists in the removal of the tarsus and in the formation of a new fornix.

MacCallan's operation

The lid spatula is placed below the eyelid to be operated on and the border of the lid is seized by the assistant with forceps and still further everted on the spatula. A horizontal incision is then made through the conjunctiva throughout the width of the eyelid about 5 or 6 mm. from the margin of the lid, i.e. in the situation in which it is desired to make the next fornix: an incision is made at each extremity of the first incision to unite it with the inner and outer canthi, stopping short 1 or 2 mm. from the lid margin. The conjunctiva is then dissected from the subjacent fascia and cartilage as far as the margin of the eyelid. The cartilage is then removed with scissors, together with as much redundant conjunctiva as is considered advisable. A threaded needle is entered from the skin surface 5 mm. below the lashes, through the tissue of the lid and through the anterior edge of the conjunctiva. It is then passed forwards through the posterior edge of the conjunctiva, coming out of the skin near to the point of entrance of the needle. Three such sutures are inserted and tied loosely. The result of this operation for the condition described is remarkably good. The stitches may be removed on the fourth or fifth day. It is important that the skin should be carefully sterilized with solution of iodine and that non-absorbable material, such as silkworm gut, should be used for the sutures.

(d) *Acute Conjunctivitis*

In the East trachoma is often complicated by acute bacterial conjunctivitis. The causal organism may be the gonococcus, the Koch-Weeks bacillus, the staphylococcus, streptococcus, pneumococcus, or the diphtheria bacillus. Clinically it is impossible to distinguish these types; any one of them may produce a membranous condition simulating

Causal organisms

a diphtheritic infection. The microscopical examination of stained films cannot differentiate the diphtheria bacillus. Cultures should always be made in suspected cases, and if possible animal experiments carried out in order to confirm the culture results.

*Diphtheria
antitoxin*

Whenever there is real suspicion that the membranous conjunctivitis is due to the diphtheria bacillus, diphtheria antitoxin should be administered in maximal dosage.

If it is impossible to evert or even to open the eyelids, canthotomy or canthoplasty should be performed immediately. On no account must the eye be occluded with pad and bandage.

If it is possible the conjunctiva should be painted twice a day with solution of silver nitrate 2 per cent. The conjunctival sac should frequently be irrigated with a gentle stream of fluid, either eusol solution 1 in 10, mercuric chloride 1 in 5,000, or potassium permanganate 1 in 5,000. If possible the irrigation should be nearly continuous, and two nurses should be employed. When silver nitrate solution cannot be applied, acriflavine 1 in castor oil 1,500 may be used, several times a day.

*Treatment of
ulceration*

The occurrence of ulceration of the cornea does not call for any change in the treatment. It is rarely advisable to cauterize the edges of the ulcers; if, however, they are sloughy they may be scraped with a small sharp spoon. The pupil may be dilated with solution of atropine sulphate 1 per cent; if the ulcer perforates, the pupil will immediately contract and the iris may, if the ulcer is not central, prolapse into the breach of the cornea thereby plugging the wound. This is to be hoped for. Then the mydriatic should be stopped as a desirable result has been obtained, for the adherent iris will vascularize the edges of the ulcer and lead to repair with the formation of an adherent leucoma. Experience has shown that after the formation of an adherent leucoma the development of secondary glaucoma is very common. Unless therefore the patient can be kept under continuous observation, a prophylactic iridectomy should be performed.

In the case of a child it may be advisable to fasten each hand to the side of the bed, quite loosely, in order that the child shall not rub the eyes. If the discharge from the eye is very tenacious, the conjunctival sac may be carefully cleaned with a little weak hydrogen peroxide solution.

In the case of adults there should be by the side of the patient a bowl of weak antiseptic solution, and a dish of cotton-wool, with which the discharge is constantly being washed away.

It is much easier to look after a patient with acute purulent conjunctivitis if he sits in a chair by the side of a table than if he is kept in bed.

(4)—Conclusion

Treatment of trachoma is disappointing since cauterizing drugs applied to the conjunctiva reach only the superficial layers, and in

all cases of more than short duration the morbid changes have extended to the pretarsal and tarsal tissues. When this has occurred the only means of obtaining a permanent cure is by an operation which can only justifiably be entrusted to an experienced ophthalmic surgeon. The operation of combined excision of the tarsus and its over-lying conjunctiva, or tarsectomy, not only removes all the diseased tissue but eliminates the ptosis of the upper lid which is present to some degree in most cases of long-standing trachoma (MacCallan, 1936).

It has recently been stated that sulphanilamide and its congeners have a beneficial effect on trachoma and that they inactivate the trachoma virus. It is clear, however, that they cannot remove the new fibrous tissue which pervades and thickens the pretarsal and tarsal structures and which specially characterizes trachoma. *Sulph-anilamide*

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TRANSFUSION

See BLOOD TRANSFUSION, Vol. II, p. 530

TRAVEL-SICKNESS

BY JOHN HILL, M.D.

SHIP SURGEON, CUNARD WHITE STAR LTD.

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Reference may also be made to the following titles:

AVIATION (MEDICAL EXAMINATION OF PILOTS)
VERTIGO

1546.] Of the disorders affecting travellers by air, land, or water, the most familiar is sea-sickness, which will serve as a typical example. Other types of travel-sickness arising from certain conditions call for special mention. Tests designed to assess the suitability of an individual to adopt the career of an air-pilot are described in Vol. II, p. 241.

1.—AETIOLOGY

Movement Movement is a *sine qua non*. At sea and in the air it often takes the form of complex and irregular oscillations, of which the vertical component is the most disturbing; in a train or car the movement is vibratory and of smaller amplitude and greater frequency. There are exceptions in some highly-sprung modern cars, in which vibration may be replaced by a swinging roll. Vibration being a milder form of abnormal stimulation than oscillation, those liable to train- or car-sickness can hardly expect to escape at sea or in the air.

In addition to movement, many contributory factors must be recognized which are so numerous that they are never all found together. Their importance in treatment consists in the extent to which they can be minimized or prevented. *Contributory factors*

Factors operating before journey begins

Extreme susceptibility is found in some who are unjustly accused of merely imagining they are ill. Such people turn giddy while dancing, have suffered sickness in childhood when playing on swings, and may be upset by any form of travel. They are usually of the nervous delicately-organized type. When groups of travellers go on a journey together it is not always the novice who is the first to succumb; this shows that susceptibility is a more important causal factor than lack of experience. *Extreme susceptibility*

Fear of sea-sickness is a common failing, induced by past experience or the accounts of others who have suffered, and is often aggravated by a fatalistic expectancy. *Fear of sickness*

Emotional excitement is often inseparable from departure on an ocean voyage and applies even more to journeys by air. Flying is still a novelty to many. Whether the air-traveller is pressed for time or merely in search of a new experience, his nervous system is in a state peculiarly adapted to the development of travel-sickness. Fatigue is very common, and often enhances the effect of other aetiological factors. *Emotional excitement*
Fatigue

Conditions of disturbed metabolism readily contribute to travel-sickness. Among these are diabetes mellitus, migraine, cyclical vomiting, chronic nephritis, and pregnancy. *Disturbed metabolism*

Factors operating after journey has begun

To these contributory factors are now added various secondary effects of the primary factor, movement. Static changes in the abdominal organs, perhaps combined with muscular efforts at adjustment, constitute a factor which is not yet fully understood. The importance of the labyrinths in travel-sickness is generally acknowledged, but attempts to prevent their influence by swinging cots and sprung head-rests have not been wholly successful. *Secondary effects of movement*
Abdominal
Labyrinthine

Ocular fatigue is common. Extreme liability to train- or car-sickness suggests the presence of an uncorrected error of refraction. The preference among railway passengers for a seat facing the engine is probably based upon the influence of ocular stimuli. Victims of train-sickness feel better when they refrain from looking out of the carriage window, especially at near objects such as fences or telegraph poles bordering the track, or other trains moving in an opposite direction; but distant scenery, if it offers interest and variety, may provide salutary distraction for the apprehensive mind. *Ocular*

In rough weather at sea, disturbing auditory stimuli arise from the noise of waves, the creaking of beams, and numerous other accompanying sounds. These are apt to induce uneasiness, if not fear, in nervous *Auditory*

people. The perpetual rumble of a train, in which it becomes difficult to converse in ordinary tones, inevitably results in fatigue of the nervous system on a long journey.

Olfactory

Olfactory stimuli are legion. Few are more upsetting than hot engine oil, kitchen garbage, or the rancid effluvia that betray the sickness of others. Even odours normally agreeable, such as those of fresh cooking, or the pungency of oranges or cigar-smoke, will sometimes determine the onset of nausea. Faulty ventilation exaggerates the effect of olfactory disturbance and may produce its own dire consequences. A defective exhaust-pipe allows the escape into a closed car of enough carbon monoxide to produce headache, vertigo, nausea, and even vomiting, while still unrecognized by the occupants. Petrol vapour causes identical symptoms. Most modern cars provide adequate air-supply without draught and rarely need to be entirely closed.

Defective ventilation

Changes due to high altitudes

Deficient oxygenation may arise during flights at high altitudes. Sudden changes in atmospheric pressure cause unpleasant symptoms of vertigo, tinnitus, and deafness, but these are usually of short duration.

Toxaemic states

General conditions such as toxaemia from constipation or indiscretions of diet are contributory causes more avoidable than the others just mentioned.

2.—BIOCHEMISTRY

*Blood-sugar
Ketosis*

Certain metabolic changes commonly occur in sea-sickness but whether they are cause or effect has still to be proved. Blood-sugar tends to rise at first and become subnormal later, but these findings vary. Ketosis from incomplete oxidation of fats is more constant; it may be due partly to starvation but has been found even in the absence of vomiting.

Deficient oxygenation

The respiratory rhythm is often irregular, rapid shallow breathing being periodically interrupted by a deep inspiration, particularly during the send of the ship. The onset of unexplained sighing or yawning during rough weather is another significant omen. As a result of respiratory changes, the pulse-respiration ratio tends to be greater or less than normal. Such changes may well play a part in, or constitute the outward manifestation of, deficient oxygenation and diminution of alkali reserve. The important part played by oxygen may be deduced from the fact that among those relatively immune to sea-sickness are found two very different groups, athletes and habitual drinkers; each has in a different way acquired the power of rapid oxidation.

3.—CLINICAL PICTURE

Travel-sickness tends to manifest itself clinically as autonomic imbalance. The predominant element is sometimes the vagus (para-sympathetic) and sometimes the sympathetic, but more often both are combined. Cases cannot be rigidly classified as vagotonic and sym-

patheticotonic because clinically they do not always fit conveniently into these twin pigeon-holes. The terms when used here should be interpreted in a relative sense. Most cases can be assessed with reasonable accuracy by a careful study of symptoms and signs.

Nausea and vomiting are commonly bracketed together, but either may occur alone. Early onset of nausea, perhaps accompanied by dryness of the mouth, and increasing in severity until followed by vomiting, which even although repeated fails to relieve it, points to sympathetic activity. When vomiting is a comparatively late sign, preceded by salivation but little or no nausea, occurring suddenly and without much effort, and followed by at least temporary improvement in well-being, predominance of vagus action may be presumed.

Nausea and vomiting

Headache may occur in all types. In those of a vagotonic tendency it is often an early and persistent symptom; in sympatheticotonics it more commonly follows nausea and vomiting. Headache often coincides with vertigo and is sometimes associated with photophobia. It is usually frontal but in vagotonia may be vertical, temporal, or occipital.

Headache

Dizziness is a common complaint in sea- and air-sickness but much rarer in train- or car-sickness. True vertigo may occur, originating in labyrinthine, optic, oculomotor, gastric, or vasomotor disturbances. More commonly the complaint refers to a sense of confusion and difficulty in muscular co-ordination. I have never known a patient to fall through the vertigo of sea-sickness. In this and other respects it closely resembles Freud's description of the vertigo of an anxiety neurosis.

Vertigo

Whereas restlessness and excitement indicate sympathetic activity, extreme lassitude is common in sea-sickness of the vagal type. The combination of physical and mental depression must be distinguished from the fatigue induced, even in immune subjects, by the difficulty of walking about in rough weather.

Lassitude

Circulatory changes are detected most easily in the pulse-rate. When vagus activity predominates the recumbent rate is commonly from 60 to 70; in sympatheticotonic cases it is more likely to be about 80.

Circulatory changes

Blood-pressure usually tends to fall or rise according as the vagus or sympathetic is the more active. Mercurial instruments are useless in stormy weather, and sphygmomanometry under conditions leading to any form of travel-sickness is manifestly liable to inaccuracy. A rough indication of the blood-pressure is furnished by the increase in pulse-rate when the patient sits up after lying down. In health, after the brief acceleration caused by the effort of rising and lasting about ten seconds, the increase is seldom far removed from 10 per cent of the original rate. In so far as it exceeds this figure, the blood-pressure is likely to be lower than normal. The effects produced by sympathetic activity are more variable.

Blood-pressure

Vasomotor instability is a feature of most forms of travel-sickness. Flushings alternating with pallor and cold sweats are common. The onset of an attack in which vagus activity predominates produces in slow motion the features of vaso-vagal syncope, namely, slow feeble

Vasomotor instability

pulse, low blood-pressure, sense of 'dizziness', confusion, faintness, and extreme pallor, indicating failure of vasomotor co-ordination and inducing an urgent desire for the horizontal position, often with the arms raised above the head. It is because of this last tendency that experienced sufferers 'prefer' sea-sickness to air-sickness of equal duration because in an aeroplane there are fewer facilities for lying down. These signs may appear before there has been any vomiting or even much nausea.

4.—COURSE AND PROGNOSIS

*Spontaneous
recovery*

Spontaneous recovery is the rule, but in some cases the symptoms persist until the return to land. Even if the most careful treatment apparently fails to shorten the duration of sickness, it may at least alleviate the discomfort. Prognosis depends largely upon the control of contributory factors. The most difficult of these is the common attitude of fatalistic resignation which makes some cases hopeless in more senses than one.

Sequelae

Certain sequelae occur, especially when sickness is prolonged. Such are globus hystericus, jaundice, or gastritis set up by repeated vomiting. Cystitis may follow a period of concentration of the urine. After landing there is sometimes a return of ataxy, due to failure of locomotory re-adjustment.

5.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

*Importance of
differential
diagnosis*

The assumption that sickness in rough weather is due to sea-sickness is fraught with possibilities of serious error. The manifold causes of nausea, vomiting, headache, vertigo, or drowsiness must be continually kept in mind. Apart from abdominal emergencies, the two conditions most commonly mistaken for sea-sickness are alcoholic gastritis and a blend of anxiety and fear resulting in a neurosis which is almost indistinguishable from true sea-sickness. In children sea-sickness rarely lasts long. Continued symptoms should arouse suspicion of ketosis, digestive upset, constipation, or acute appendicitis. Sometimes the cause is psychogenic; the child is made ill by fear of the unseen bogy that has prostrated his mother.

To most people sea-sickness means nausea and vomiting, with the result that sufferers from headache or lassitude sometimes fail to suspect the origin of these symptoms.

6.—TREATMENT

(1)—Preventive

The first step in prevention is to exclude or minimize as far as possible the contributory factors already enumerated. For an ocean voyage

early booking is advisable so as to reserve a well ventilated cabin as nearly as possible amidships, and comfortably remote from disquieting noises and the smell of cooking. Accommodation at the ship's side is usually at a premium, but an apprehensive passenger travelling at a time when rough weather is to be expected will find that an inside cabin, provided the ventilation is good, offers more freedom from the noise of wind and waves. *Shipboard accommodation*

The most comfortable motor cars are those with the rear seat well within the wheel-base. Boredom often contributes to car-sickness, especially in children, to whom enforced inactivity quickly becomes irksome. It may be obviated by engaging conversation or interesting scenery, provided vision is not blurred by fixation on near objects. The vigilant concentration essential to safe handling of a car provides one reason why car-sickness never affects the driver. *Car-sickness*

Before and after starting on a sea voyage adequate rest should be enjoined. This advice will seldom be popular, but it is well to point out that among single avoidable factors contributing to travel-sickness fatigue is the most powerful. Passengers exhausted by the strain of preparation for a voyage, culminating in wearying farewells and late nights, often rely on the sea air to restore their energy. But they are in no condition to withstand the effects of rough weather. Rest is particularly important for the digestive organs. Diet should be reasonably light, with ample carbohydrate and little fat. Constipation and drastic catharsis should both be avoided. *Avoidance of fatigue*

Preventive treatment by drugs is determined to a large extent by the length of the contemplated journey. If this is measured in hours, an appropriate dose of some quickly acting and transient narcotic, such as sodium amytal or nembutal, may meet the case. But for a voyage lasting days or weeks the requirements are not so simple, and it is then important to have some previous knowledge of the patient and his probable response to the ship's movement. *Drugs*

In proportion to the patient's nervousness preliminary sedation is advisable. During the twenty-four hours before sailing, bromides up to 60 grains and chloral hydrate 20 to 30 grains may be taken in divided doses at suitable intervals. Physical lassitude which sometimes follows these large doses may be countered by the addition of 10 to 15 minims of tincture of nux vomica. Barbiturates are more palatable and convenient but their action is less certain. Sedative drugs, apart from their physiological action, allay uneasiness. Phlegmatic subjects should have atropine sulphate $\frac{1}{120}$ to $\frac{1}{60}$ grain, hyoscine hydrobromide $\frac{1}{240}$ to $\frac{1}{80}$ grain, or tincture of belladonna 10 to 20 minims, similarly divided. Most patients require a suitably balanced combination of a central nervous sedative and a vagus inhibitor. *Sedation*

The value of most proprietary remedies lies in the faith of those who use them. This is not to impugn the honesty of their manufacturers. If the proprietary medicine is not entirely worthless it must contain some fairly potent drug which, to be safely sold to the public, must *Stimulation*
Combined treatment
Stock remedies

be in such cautious dosage that the amount taken by the purchaser is almost certain to be inadequate.

The practitioner who prescribes any remedy for sea-sickness to be taken before or after sailing will be well advised to inform the ship surgeon of the ingredients, lest alternative treatment be required.

*Preventive
measures
after sailing
Diet*

Fresh air

Exercise

Preventive treatment after the ship has sailed should include continuance of the measures already recommended. Moderation in eating and drinking is extremely important, if for no other reason than that anxiety will have curtailed the digestive capacity. Dietetic principles are discussed as part of specific treatment (see p. 229). Fresh air is invaluable but must not be obtained at the expense of body warmth, because in sea-sickness the thermogenic function quickly becomes impaired. If fresh air can be combined with exercise, both heat production and respiratory exchange are thereby encouraged, and healthy distraction will be offered to the mind haunted by dread and uncertainty. But exercise should be forbidden just before and after meals and must at all times stop short of fatigue.

(2)—Specific

*Vagotonia
Belladonna
group*

*Adrenaline
Ephedrine
Benzedrine*

Caffeine

Exercise

With the onset of sea-sickness the various types usually begin to be more clearly distinguished. In cases showing vagotonia therapeutic doses of atropine, hyoscine, or tincture of belladonna are indicated and should be repeated as may be required; these patients often show considerable tolerance. Autonomic balance may be restored also by stimulation of the sympathetic. The action of adrenaline is too abrupt and evanescent for this purpose. Ephedrine is useful, but recently benzedrine sulphate in doses of 5 to 10 mgm. has been found even more satisfactory, particularly on account of its action on the higher centres in overcoming morbid languor. The drug is easily retained and its effects appear within half an hour. It may be given in solution, combined with other drugs; if vomiting persists it may be given in the form of a suppository, and then two or more hours are needed for its absorption. When powerfully sympathetotropic drugs are used, glucose should also be given to maintain the blood-sugar level. High blood-pressure and undue excitability of the nervous system contra-indicate the use of benzedrine. Caffeine is another valuable stimulant to the nervous system, either medicinally or as strong tea or coffee.

If the patient is not too far gone in sickness to make the effort, exercise in the fresh air will be beneficial. Even below decks in bad weather short periods of exercise may be advantageously alternated with rest in the horizontal posture. Alternatively, a cold or tepid bath will stimulate respiration and the vasomotor system.

For the treatment of increased sympathetic activity, a host of remedies are available. Few are more reliable than repeated doses of bromide and chloral hydrate. A useful prescription consists of potassium bromide 60 grains, chloral hydrate 20 or 30 grains, in one fluid ounce of water, flavoured as desired. The dose is one teaspoonful every half-hour.

Small repeated doses favour retention and absorption. The suggestibility of this type of patient gives an added value to the insistence upon frequent and regular repetition. Over-dosage is prevented by the fact that when the needs of the condition have been met and the patient becomes drowsy the intervals are automatically lengthened. There is a specific curative value in sleep. Among the barbiturates, soluble pheno-
barbitone, soluble barbitone, prominal, and dial have proved successful, but their effects vary. They are best given in cautious dosage until the absence of idiosyncrasy is proved. *Barbiturates*

If vomiting persists in spite of these measures the lower bowel should be cleared out if necessary and potassium bromide 60 grains with chloral hydrate 20 grains in about 6 fluid ounces of warm water given slowly *per rectum*. For the individual case hypodermic medication has obvious advantages, but it is rarely feasible when a number of patients have to be seen at frequent intervals. *Sedatives per rectum*

Valuable adjuncts to sedative treatment are those drugs with a stimulant action on certain portions of the parasympathetic nervous system. Physostigmine salicylate $\frac{1}{100}$ to $\frac{1}{50}$ grain hypodermically can do much to restore normal gastro-intestinal function. It is of most value if combined with acetylcholine, nature's own stimulus to parasympathetic activity, 0.1 gm. in fresh solution, intramuscularly. Acetylcholine bromide is stable in aqueous solution. Nitrites are traditionally useful in some cases, and so too is glyceryl trinitrate (trinitrin) which has the same physiological action. The tablets must be fresh and are more effective if allowed to disintegrate slowly under the tongue than if swallowed. *Physostigmine Nitrites*

Alcohol is sometimes valuable; it probably has some reflex stimulant action, followed by dulling of the hypersensitive nerve centres. No definite rules can be laid down; champagne has many advocates, and so has brandy. Dry ginger ale seems just as effective as either, and yet whisky and soda is often worse than useless. Much must depend on individual habit and susceptibility. Opiates are on the whole disappointing; their action in sea-sickness varies, and even temporary benefit is apt to be undone by unpleasant after-effects. *Alcohol Opiates*

The types here described are extremes, and therefore exceptional. In the average case symptoms point to disturbance of both divisions of the autonomic nervous system, and treatment must be judged accordingly. Belladonna, bromide, and chloral hydrate, in appropriate doses, are of more constant value than any other combination known to me. *Combined treatment*

At various stages in the treatment of sea-sickness the matter of diet must be decided. Unaccountable tastes and dislikes are common, and the predilections of the patient, however capricious they may seem, are often a better practical guide than the most erudite hypotheses. Certain general principles, however, may be outlined. Small amounts of food at frequent intervals, chewed thoroughly and eaten as slowly as is compatible with social usage, will turn vagus activity to good account. If this is lacking and anorexia is complete, glucose should be given, in *Diet*

strained orange juice, for example, or in 5 per cent solution as an enema.

*Alkaligenic
diet*

If circumstances warrant a more ambitious dietary, the maintenance of normal acid-base equilibrium would seem to be best assured by an alkaligenic diet consisting largely of fruit and vegetables, supplemented by milk if it agrees. Animal food need not be wholly forbidden. Fatty dishes, and those of elaborate or uncertain composition, are best left to the seasoned sailor. The patient may choose according to taste from small portions of clear soup, hot or cold; cold chicken, ham, or beef without gravy; baked potato; dry toast or the like; and small cups of tea or coffee. A salt-free diet has been held to favour the absorption of bromides. A lacto-vegetarian diet needs little additional fluid.

Fluids

Restriction of extra fluid at meal-times ensures better mastication. On the other hand, although dry meals are retained and digested better than liquid, vomiting may have produced some dehydration which must first be remedied. Sucking ice is an agreeable method.

(3)—Symptomatic

*Abdominal
binder*

Distressing abdominal uneasiness is often greatly relieved by a broad binder, such as a bath-towel, fastened firmly from the pelvis to the ribs, or by a mustard plaster over the epigastrium. The same effect can be produced by ventral decubitus with a pillow under the abdomen, or by deep breathing, taking a full inspiration with the send of the ship.

*Aperients
Glucose and
insulin*

Some vagotonic individuals have an initial diarrhoea, but as a rule constipation requires treatment. In persistent vomiting a sodium nitroprusside test of the urine may reveal ketosis, for which glucose and insulin should be given; otherwise chlorbutol (chlortone) 10 or 15 grains in capsule or cachet may be tried. Irritability of the gastric mucous membrane may yield to cerium oxalate or the traditional bismuth mixture.

*Chlorbutol,
cerium
oxalate, and
bismuth*

TREMATODE INFESTATION

See BILHARZIASIS, Vol. II, p. 323; CLONORCHIASIS, Vol. III,
p. 248; FLUKE INFECTIONS, INTESTINAL, Vol. V, p. 320;
and PARAGONIMIASIS, Vol. IX, p. 401

TREMOR

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Reference may also be made to the following titles:

ALCOHOLISM	PARALYSIS AGITANS
HEPATO-LENTICULAR	TOXICOLOGY:
DEGENERATION	INDUSTRIAL POISONING

1.-DEFINITION

1547.] Tremor is a spontaneous involuntary rhythmical alternating contraction of a group of muscles and its antagonists. The spontaneity of this kind of involuntary movement might well be assumed but needs emphasis in a definition otherwise equally applicable to so dissimilar a movement as clonus, for which some degree of external interference is necessary. Although fibrillation (see Vol. V, p. 276) is often called 'fibrillary tremor', it is not related to the present subject in either origin or nature, as the definition makes clear. Tremor of the face and tongue can hardly be said to be the result of movements of protagonists and antagonists because of the special character of the musculature. It is, however, impossible to doubt the clinical identity of tremor in these situations with other forms for which this definition is accurate.

2.-AETIOLOGY

Tremor occurs in many conditions during health. If a part of the body *In health* is held rigidly fixed by the strongest contraction of its muscles it is

- Fatigue* affected with a fine tremor, the extent of which varies in different subjects. Physiological tremor in response to cold is well known and most people have experience of the tremor of emotion, either from fear, excitement, or anger. Fatigue is not so generally appreciated as a disposing factor although its effects are no less obvious. In addition, some healthy persons react with abnormal facility to physiological causes and may tremble for no clear reason. Tremor may be continual throughout life and occasionally exhibits a marked familial incidence. Some degree of tremulousness is natural in old age.
- Infections* Tremor is a not uncommon symptom of acute infections, particularly enteric, typhus, and influenza, either during their course or for many weeks after the convalescent stage has been reached. Of the more chronic infections tuberculosis has long been believed to favour the occurrence of tremor. Any form of over-activity of the thyroid causes tremor. Even in severe thyrotoxicosis there is sometimes not any clinical enlargement of the gland, 'masked hyperthyroidism', and the diagnosis must be reached from systemic symptoms of which tremor may be the most striking to both the patient and practitioner. Tremor is a feature of many extrinsic intoxications. Alcohol and tobacco are common causes and even in moderate amounts may be responsible, although in this, as in other effects, individual susceptibility plays a large part. In chronic mercurial poisoning, a rare industrial disease, wide-spread tremor is usually the earliest complaint and has long been emphasized by the workers, who describe the illness as 'the trembles'. It is seen in persons employed in quicksilver mines or in factories where the metal is handled in liquid form for the manufacture of mirrors, barometers, and thermometers. Rarely tremor is one of the first symptoms of lead-poisoning. Mercurial tremor is hardly known except in industrial poisoning, although in the past mercury was used medicinally in quantities purposely calculated to cause severe stomatitis. To-day bromide and thyroid are the common therapeutic agents most likely to be associated with tremor, the symptom being especially prominent in bromism. In each an unrecognized susceptibility to ordinary dosage is the usual reason for the development of intoxication.
- Intrinsic*
- Extrinsic*
- In psychoneuroses* As fear is the predominant emotion of most psychoneuroses, trembling is a common accompaniment of this kind of illness. In anxiety states it is seldom absent, being indistinguishable from the fine rapid irregular tremor of the healthy person in moments of mental stress. In hysteria the wildest and most varied tremors are seen, particularly if an attempt is made to examine an affected part. The generalized almost convulsive tremblings of those who suffered from shell shock (war hysteria) may recur in civil life in a later break-down whatever its immediate cause.
- Tremors of organic disease of the nervous system must be distinguished clinically from those already described and from one another. More than a hundred years ago James Parkinson described the tremor which bears his name. The quality of the tremor is the same in the long-familiar form of the disease of which Parkinson wrote (paralysis agitans) and

in the form which follows encephalitis epidemica. In each there are identical defects of muscular tone and movement, now known to depend on disease of the extrapyramidal motor system. Similar tremor and dystonia occur in hepato-lenticular degeneration (Kinnier Wilson's disease) in which the same system is destroyed. In disease of the cerebellum, shaking of a different character is constantly present. Lesions of the mid-brain are sometimes associated with pronounced tremor and rarely the symptom may follow ordinary hemiplegia; such post-hemiplegic tremor is confined to the arm and occurs chiefly on voluntary movement. Its rarity and its universal absence in the totally paralysed limb are features calling for special notice. Irregular quivering movements of the face, tongue, and hands are usual in dementia paralytica.

*Cerebellar
disease*

Hemiplegia

*Dementia
paralytica*

3.—PATHOGENESIS

Little is known of the exact mechanism of tremor in the forms depending on organic nervous disease and there is not any information about morbid changes in other kinds. Lesions of the old (extrapyramidal) motor system and of the cerebellum each lead to tremor, associated in the one case with raised and in the other with lowered tone in the affected muscles. The state of muscle-tone cannot therefore have any connexion with tremor; moreover, Walshe has shown that Parkinsonian tremor is uninfluenced by rendering muscles flaccid with injections of procaine hydrochloride (novocain). Theoretically, involuntary movements of any kind may be caused either by irritative stimulation of nerve-cells or by the removal of inhibition from higher levels with consequent release of lower centres resulting in spontaneous activity. In all forms of striatal disease the appearance of the lesions suggests neuronal destruction. It may therefore be argued that the symptoms are due to the uncontrolled activity of lower centres. Conversely, the fact that the tremor of Parkinsonism endures for years, sometimes without alteration, makes the supposition that it is caused by irritation inconceivable. From its nature, tremor seems to be the product of a lower nervous centre. It is systematized and capable of only slight variation, directly opposite qualities from those of movements arising at higher levels. From arguments of this kind Kinnier Wilson concluded that tremor is 'the expression of an inherent property of neurocellular activity' and that 'its mechanism . . . is controlled by an involuntary prespinal centre or centres at the general level of corpus striatum, cerebellum and mesencephalon'.

*Removal of
inhibition
from higher
centres*

4.—CLINICAL PICTURE

Clinical forms of tremor are distinguished by difference in rate, range, and rhythm. The localization and any factors influencing the movements

*In general
medicine*

are also worthy of notice. Most kinds of tremor, except those caused by striatal or cerebellar disease, have a rapid rate, a fine range, and an irregular rhythm. In these characters alone the tremor of cold or of post-influenzal debility cannot be distinguished from that of an anxiety neurosis or of intoxication by tobacco. In all forms tremor tends to be most easily seen in the upper limbs, particularly if these are held out straight and stiff with the fingers fully abducted. Strong simultaneous contraction of agonist and antagonist groups of muscles reveals some degree of tremor even in healthy persons, and the test of the outstretched arms makes use of this physiological method of releasing tremor in order to exaggerate the morbid kinds.

Amplitude

The finest and most rapid tremor is found in mild degrees of hyperthyroidism and in anxiety neurosis: indeed, the range may be so small that the movement is invisible and can only be detected by palpation. The tremor of extrinsic intoxications is usually coarser, particularly in mercurial poisoning and delirium tremens, but in the more chronic form of alcoholism and in poisoning by tobacco the amplitude may be only moderate or even fine. In a severe case of toxic goitre the movement may be coarse. In hysteria the character of the tremor changes abruptly at short intervals, an extravagant shaking of a limb or of the whole body being suddenly substituted for the delicate rapid fluttering first observed.

*In organic
nervous
disease*

*In
Parkinsonism*

In marked contrast, the tremors of striatal or cerebellar disease have a constancy of quality, even from case to case. Parkinsonian tremor is slow, the movements being repeated at the rate of from four to eight a second. It is remarkably regular and is nearly always more evident in resting muscles. This almost clock-work rhythm is perhaps more valuable in diagnosis than any other feature. The range alone varies widely, from being so fine as to be hardly visible to a wide excursion of several inches. By contrast, the tremor of cerebellar disease is only seen during active movement, at least in the early stages, and becomes more exaggerated the greater the voluntary intent towards muscular precision. The terms 'action tremor' and 'intention tremor' are therefore used in description and the many tests employed all aim at compelling great accuracy of voluntary movement. In advanced disease of the whole cerebellum tremor may occur in apparently resting muscles, particularly of the head and neck. These movements are called 'titubation' and are slow, irregular, and often of wide amplitude. They are best seen if the patient tries to sit or stand erect, conditions in which the musculature of the neck and trunk is far from being in a truly resting state.

*In cerebellar
disease*

The situation of a tremor is of value in determining its nature. Senile tremor first affects the hands, but soon after the head is also involved. Irregular trembling of the tongue and of the muscles about the mouth is rarely absent in cases of dementia paralytica and alcoholism. In the former the classical coarse 'trombone' tremor of the tongue may be seen, but not as often as some older descriptions suggest. Mercurial

tremor begins in the face and tongue, later involving the upper and lower limbs in that order. In Parkinsonism those parts in which rigidity is greatest are least likely to exhibit tremor, and this accounts for its predominance in the smaller more peripheral muscles of the upper limb. The proximal parts of the limbs and the head and neck are not affected until late in the disease and may escape entirely, although any muscle-group and its antagonists may be affected. In most cases of Parkinsonism both tremor and rigidity begin on one side of the body and may remain worse there throughout. The tremor may move from one group of muscles to another while the patient is being watched. The typical 'pill-rolling' movement of the fingers and thumb suddenly ceases and may be replaced by a pronation-supination of the forearm, which in its turn gives way to flexion-extension of the wrist.

*Of
Parkinsonian
tremor*

The tests used clinically to exaggerate tremor have been mentioned. It may also be inhibited in certain circumstances. All tremors cease after complete paralysis of the involved parts, as shown by the sudden cessation of wild involuntary movements in a Parkinsonian developing an intercurrent pyramidal hemiplegia. Deep sleep and coma act similarly. Parkinsonian tremor may be inhibited for a short time by the application of a painful stimulus, and sometimes by changes in posture. Sudden emotional shocks sometimes inhibit Parkinsonian tremor temporarily. If the patient tries to control his tremor by an effort of will, he may be partially successful for a few minutes, but the movement tends to recur more violently when the attempt is abandoned. The tremor of chronic alcoholism improves or even vanishes temporarily after further consumption of alcohol. Anxiety increases all forms, the patient often being at his worst when he visits the doctor. Tremor of the face and tongue is usually exaggerated by voluntary contraction of the muscles, particularly if this is submaximal. Recently developed senile tremor only occurs with voluntary movement, but later the trembling persists when the muscles are resting.

*Factors
influencing
tremor
Inhibition*

Exaggeration

Senile tremor

5.—COURSE, PROGNOSIS, DIAGNOSIS, AND TREATMENT

The course, prognosis, diagnosis, and treatment of tremor must in the main be those of the diseases causing the symptom.

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TRENCH FEVER

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Reference may also be made to the following title:

ARTHROPODS AND DISEASE

1.—DEFINITION

(*Synonyms.*—*Fièvre des tranchées*; *Fünftagefieber*; febris wolhynica, febris quintana)

1548.] Trench fever is, or rather was, a mystery disease. It was first detected during the spring of 1915 among soldiers fighting in the trenches on the Western Front, and after less than four years of great prevalence it suddenly disappeared. The disease must have existed before 1914, but where and in what form is not known. Probably it still exists in an 'inapparent' form but no cases of natural infection have been reported since 1918.

Trench fever was a febrile disease probably caused by *Rickettsia quintana* and conveyed from man to man by human lice. The only characteristic clinical feature was the tendency of the fever to occur in spells, at intervals of five or six days, but as this periodicity was only observed in a minority of the cases it is impossible to give a precise definition of the disease.

The first account of the disease was contained in a report of two cases in British soldiers by J. H. P. Graham in September 1915. The

disease spread rapidly all over the Western Front and W. Byam estimated that 20,000 cases occurred among British troops between July 1917 and July 1918. Numerous cases were reported from Salonika and a few from Egypt and Mesopotamia. The disease was prevalent among all the troops on the Western Front but there is no reliable evidence of the number of cases which occurred in the French and German armies. Except for experimental cases and a few isolated cases the disease was confined to soldiers living in conditions of heavy louse infestation in the trenches and to personnel coming in contact with these men on the lines of communication. The disease at first tended to be mild and of short duration but it gradually became more severe so that during the last two years of the war the average period of hospitalization was two and a half to three months.

History of the disease during the World War

2.—AETIOLOGY

Experimental investigation of trench fever was first carried out by McNee, Renshaw, and Brunt on twenty-one volunteers in France in 1915–16 (McNee, 1923). The blood of infected persons was found to be capable of causing the disease in volunteers by subcutaneous and intravenous inoculation. Later investigations by the Commissions of the American Red Cross and the British War Office showed that the infection might persist long after the onset, in one case up to the 200th day. The persistence of the infection in patients enabled W. Byam and his colleagues to continue the study of the disease in a special hospital in London during the year 1919, although the only fresh infections in that year were among experimental volunteers.

Experimental transmission to volunteers

McNee and others brought forward evidence in 1916 which pointed to lice as the vectors. Later it was found that lice which had fed on patients and had been kept at temperatures of 26° to 30° C. for five to twelve days could transmit the disease to human volunteers. Lice which had once been infected remained so for the rest of their lives. There was reason to believe that the virus contained in the faeces or bodies of the lice entered the human body through scratches rather than the bites of the insects.

Vector

Töpfer in 1916 showed that large numbers of rickettsia bodies (*R. quintana*) were contained in the mid-guts of lice which had fed on infected persons. These bodies were found by later workers to differ from those found in lice infected with typhus in being situated on the surface of the epithelial cells and in having somewhat different staining reactions. They also were not capable of causing disease in experimental animals.

Rickettsia bodies in lice

The virus when dried was found capable of surviving for two to four months and was able to withstand exposure to a temperature of 55° C. which kills lice and their eggs. No one succeeded in cultivating the virus *in vitro*.

*Evidence of
spirochaete
as causal
organism*

The tendency of the disease to relapse at regular intervals of five or six days suggests that a spirochaete would be the most likely causal organism: some French and German workers claimed that they had found spirochaetes in the blood of patients but the elaborate investigations of German, American, and British workers produced convincing evidence that the causal organism was a rickettsia body and not a spirochaete. Should the disease reappear in recognizable form it would be worth while to consider the possibility that spirochaetes might be concerned in the causation, as the evidence pointing to rickettsia bodies, though strong, is not absolutely conclusive.

3.—CLINICAL PICTURE AND PROGNOSIS

*Incubation
period*

The incubation period ranged from eight to thirty days. The onset was usually sudden, the temperature rising to 101° to 104° F. within 24 to 36 hours. There were intense headache and shifting pains all over the body, most severe in the shins. Chills and sweating were common and sometimes diarrhoea and vomiting occurred. In many cases the onset was indistinguishable from that of dengue or influenza.

*Skin
manifestations*

A roseolous rash was seen in many cases, consisting of pink macules or papules on the chest, back, and abdomen. The spots might be scanty or numerous and sometimes lasted only a few hours. The spleen was usually enlarged. A polymorphonuclear leucocytosis was almost invariably present during the febrile periods, usually followed by a relative lymphocytosis in the convalescent stage.

*Spleen and
blood*

Fever

The fever was exceedingly variable in duration and, although considerable irregularities occurred in the temperature curves, the fever tended to come in a succession of short spells following each other at intervals of five to six days.

Types

Most of the cases conformed to one of the following four types, of which the first three show a close resemblance to dengue. (i) A short spell of fever lasting two to six days. (ii) A spell similar to the above but followed by one to four days of apyrexia and a relapse of two to three days' duration. (iii) A 'saddle-back' type differing from type (ii) only in that the first spell had not ended before the second spell began: the whole attack lasted a week or so but in some cases there was a further period of irregular fever. (iv) A succession of three to twelve short spells of fever each lasting one to three days and recurring every five to six days; this very characteristic type of fever led to the recognition of the disease as a special clinical entity and to the designation 'five days' fever'. The total duration of the fever was thus from two days to several weeks and, as in most fevers, irregularities in the temperature curve were common. When the disease first appeared the short types predominated, but later the prolonged types were commoner and the disease became much more severe.

*'Five days'
fever'*

During the course of the prolonged cases disordered action of the

heart and depression were common and convalescence was often prolonged. In the short attacks there were few complications and convalescence was rapidly established. The commonest sequelae were neurasthenia and disordered action of the heart. The mortality was practically nil but there were many cases of prolonged invalidism.

*Complications
and sequelae*

Prognosis

4.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In places where the disease was common diagnosis was not difficult except in the short cases which often closely resembled influenza or dengue. The five- to six-day periodicity was almost the only reliable feature; in the absence of this the diagnosis was made chiefly by exclusion of other causes of fever. There must have been many cases of 'inapparent' infection judging by analogy with other febrile diseases.

The short cases were differentiated with difficulty from influenza, dengue, sand-fly fever, and mild infective jaundice when these diseases occurred in the locality, otherwise there was no likelihood of mistakes being made by medical officers with experience of the disease. In the chronic cases enteric or undulant fever might be simulated but these diseases could usually be excluded by specific tests.

*Differential
diagnosis*

5.—TREATMENT

Prevention followed the same general lines as in typhus and relapsing fever, but mere delousing was not enough because the virus in the bodies and faeces of the lice could survive temperatures at which the lice were effectively destroyed. Thorough disinfection of the clothing was needed as there was reason to believe that virus adhering to soiled clothes could enter the body through scratches.

*Preventive
treatment*

No treatment was found to influence the duration of the disease but great importance was attached to maintaining the nutrition of the patients and keeping them at rest in cheerful surroundings till convalescence was well established. After severe attacks a period of leave was of great value in restoring the patients to normal mental and physical health. Aspirin was much used to relieve the pains and insomnia which were distressing features of many cases.

*Symptomatic
treatment*

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TRENCH-FOOT

See FROST-BITE AND TRENCH-FOOT, Vol. V, p. 440

TRENCH NEPHRITIS

See NEPHRITIS AND NEPHROSIS, Vol. IX, p. 139

TRICHIASIS

See EYELIDS, DISEASES AND INJURIES, Vol. V, p. 244;
AND TRACHOMA, p. 215

TRICHINIASIS

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Reference may also be made to the following title:

PYREXIA OF OBSCURE ORIGIN

1.—DEFINITION

(*Synonyms*.—Trichinosis; trichinelliasis)

1549.] This is an infestation of man by a nematode worm, *Trichinella spiralis*, of which the adult forms infest the wall of the small intestine, whence the larvae migrate to the muscles, in which they become encysted and cause various symptoms.

2.—*TRICHINELLA SPIRALIS*

Trichinella spiralis (Owen, 1835) Railliet, 1895, was first observed as larvae in the muscles at necropsies in London by Hilton in 1833. Rediscovered by Paget in 1835, they were eventually referred to Owen,

who named them *Trichina spiralis*. Leidy found the larvae to be common also in pig's flesh, and Herbst (1851) showed that they became adult in a few days when fed to an appropriate animal, and also that the females were viviparous.

The adult worms inhabit the small intestine and, in the natural state, pigs, wild boars, and rats act as hosts, in addition to man. Under experimental conditions rabbits are insusceptible but dogs, cats, foxes, bears, martens, and all other creatures which feed on rats can become infected. Birds have so far been found to be refractory to experimental infection. Two hosts are required to complete the life-cycle of *T. spiralis*, during which each host harbours in turn the mature and larval stages of the worm.

The adult worms are attached to, or buried in, the intestinal mucosa of their host. In this situation the males impregnate the females and thereafter soon die off. At this stage the females increase to their maximal size, boring more deeply into the intestinal wall. They may work their way to the peritoneum or mesenteric lymphatic glands, and by this means the viviparously born young may be deposited in the lymphatics and possibly also in the mesenteric veins. It was estimated by Leuckart that each female produced as many as 1,500 larvae.

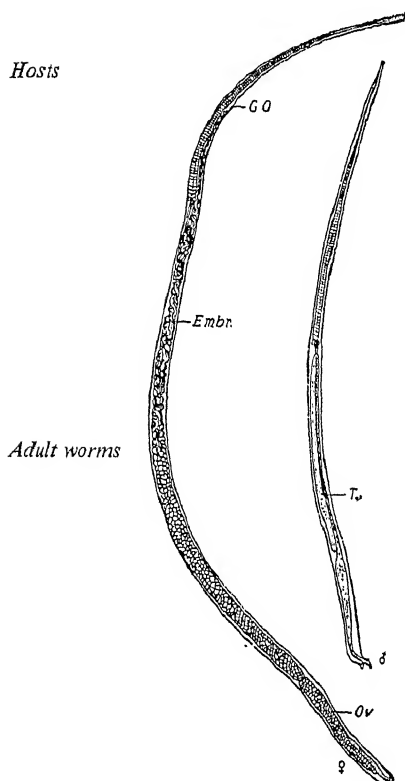
The male (see Fig. 9) is 1.4 to 1.6 mm. in length and is visible to the naked eye; the transverse diameter is 0.04 mm. It is attenuated anteriorly and broader posteriorly. The cloaca, opening at the posterior end of the worm, is evertible during coitus. The posterior end is prolonged into two conspicuous conical papillae.

FIG. 9.—*Trichinella spiralis*, ♂ and ♀, × 45. (After Brumpt.) *Embr.*, embryos; *G.O.*, genital opening; *Ov.*, ovary; *T.*, testis. (This and Fig. 10 from *Manson's Tropical Diseases*)

The female (see Fig. 9) is larger than the male and viviparous, and measures 3 to 4 mm. long by 0.06 mm. broad; the vulva is situated in the anterior fifth, and the posterior half is occupied by the ovary and a much coiled uterine tube. The anus is subterminal.

The larvae measure 90 to 100 μ in length by 6 μ in breadth. Carried passively in the lymph and blood-stream and guided by chemotaxis these larvae pierce the coats of the containing vessels and become encysted in the striated muscles, especially the diaphragm, and the laryngeal, lingual, and intercostal muscles, particularly those which are continuously active.

Between the seventh and twenty-third days after infection they are



Male

Female

Larvae

found in the arterial circulation and reach their destinations on the average about nine days later. While the female worms are in the intestinal wall, during a period of five or six weeks, a continuous stream of migratory larvae is observable.

The capsule of the cyst becomes elliptical with blunted ends (see Fig. 10). In this state the larvae remain encapsulated, but active and viable, for many years, in man, for instance, as long as thirty-one years. Often, however, they die and become calcified, but larvae which have not become encysted may reach maturity on ingestion by a suitable animal.

When infected pig's flesh is ingested by man, rats, dogs, or other carnivorous animals, the larvae become excysted in the gastric juice, pass into the duodenum and small intestine, enter crypts in the intestinal wall, and soon become mature.

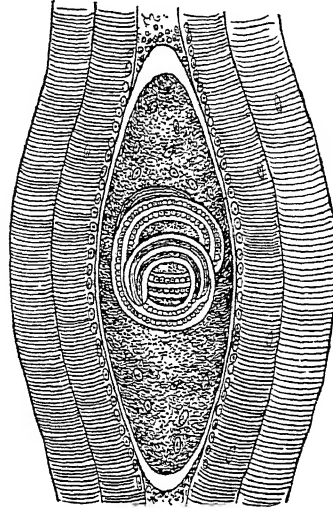


FIG. 10.—Encysted larva of *Trichinella spiralis*, fifteen days after entering muscle. $\times 300$. (After Claus in Brumpt's *Précis de parasitologie*)

3.—CLINICAL PICTURE

Trichiniasis may cause many different symptoms, and the disease is usually divided into three stages: the period of invasion, the period of migration of the larvae, and the period of encystment and consequent tissue changes.

(1)—Period of Invasion

In this stage the symptoms are mostly gastro-intestinal: nausea, vomiting, diarrhoea with dysenteriform motions, and colic, due to catarrhal inflammation of the intestine caused by the worms; sometimes haemorrhage from the bowel, brought about by the activities of the adult worms, may be noted.

(2)—Period of Migration of Larvae

This stage is characterized by pain due to the involvement of the muscles, such as the diaphragm, those of the arms and legs, the intercostals, the larynx, and the mouth, and by the resulting impaired function, such as of respiration, mastication, and phonation. The invasion of the diaphragm and intercostal muscles is usually accompanied by very distressing dyspnoea. There is often pyrexia, which may reach 104° or even 105° F. and may predominate about the second week. The fever may resemble typhoid with a slow muttering delirium. The blood changes at this stage are remarkable. There is a leucocytosis of 30,000 to 60,000, with predominance of eosinophil cells which sometimes reach 60 per cent of the total leucocytes.

Pain

Dyspnoea

Fever

Blood picture

(3)—Period of Encystment

In this stage the muscular pains are most severe, and there is considerable oedema of various parts of the body, especially the face. Cachexia, due to absorption of toxins from the larvae, is prominent. In heavily infected cases, which ultimately recover, these symptoms gradually subside.

4.—COURSE AND PROGNOSIS

Precipitin reactions

The outlook in lightly infected cases is good. In severe epidemics as many as 30 per cent of the infected persons may die.

5.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnosis by immunological reactions is employed in man and animals. In 1928 Bachman showed that positive precipitin reactions could be obtained by using extracts of the isolated parasite, but the reaction usually becomes positive too late in the disease to be of much practical use.

Preparation of antigen

An antigen is prepared from rabbits experimentally fed with cysts. About twenty days before incapsulation has occurred (i.e. about twenty days after infection) the animal is killed, and the masseter muscles are exposed to peptic digestion. The larvae are concentrated and repeatedly washed to free them from rabbit muscle. They are then dried and extracted with a 1 in 500 sodium chloride solution. The antigen injected intradermally gives two types of reaction: an immediate reaction characterized by the formation of a papule at the site of injection, and a delayed reaction which attains its maximum twenty-four hours after injection. Most American workers find that a 1 in 10,000 dilution of the antigen in Coca's solution gives the best results two to three weeks after infection.

Intradermal injection of antigen

Biopsy

In the stage of encystment, in which muscular and rheumatic pains predominate, biopsy of a small piece of muscle, such as the deltoid, the biceps, or the gastrocnemius, especially in the vicinity of the tendinous attachments, and examination under the low power of the microscope usually reveals the encysted larvae. Digestion in artificial gastric juice, with pepsin and hydrochloric acid, of suspected material, especially the laryngeal muscles, is said to give better results.

Differential diagnosis

The differential diagnosis of trichiniasis affords an interesting study, but it is one that can rarely present itself to the practitioner in Great Britain at the present time.

In the early stages trichiniasis presents certain features in common with food poisoning, cholera, and dysentery; at a somewhat later stage enteric fever must be ruled out. The oedema which has been described may be confused with nephritis, but the absence of albuminuria should settle this point. In trichiniasis there is always considerable eosinophilia, and in the secondary stage the male worms can be found in the faeces and the larvae demonstrated in the blood-stream.

6.—TREATMENT

(1)—Prophylactic

The knowledge that the pig is the main reservoir of infection for man has resulted in the almost complete disappearance of trichiniasis in man from Europe and America. The systematic examination of pig's carcasses by meat inspectors has been specially directed towards this infection and entails a microscopical examination of the laryngeal muscles and the diaphragm. The ordinary methods of curing meat or ham by salting or smoking are ineffectual for killing the larvae; refrigeration at 5° F. for not less than twenty days renders infected meat harmless, but boiling for a period of half an hour for every pound of flesh is the only really safe method.

(2)—Palliative

No therapeutic agent is specific for the *Trichinella* or will cut short the course of the disease. Only palliative measures can be used.

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TRICHOMONIASIS

See DIARRHOEA ASSOCIATED WITH FLAGELLATE INFECTION, Vol. IV, p. 15; and LEUCORRHOEA AND OTHER NON-HAEMORRHAGIC VAGINAL DISCHARGES, Vol. VII, p. 714

TRICHORRHEXIS NODOSA

See HAIR FOLLICLES, ABNORMALITIES AND DISEASES,
Vol. VI, p. 166

TRICUSPID VALVE DISEASES

See HEART DISEASES: RIGHT SIDE DISEASES, Vol. VI, p. 363

TRIGEMINAL NEURALGIA

See NEURALGIA, TRIGEMINAL AND GLOSSOPHARYNGEAL,
Vol. IX, p. 176

TRIGGER FINGER

See HAND, DISEASES AND DEFORMITIES, Vol. VI, p. 178

TROPICAL DISEASES, GENERAL SURVEY

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*Reference may also be made to tropical diseases appearing under their
own names, and to the following titles:*

ANTENATAL CARE	HEAT-STROKE AND HEAT-
CARRIERS IN INFECTIVE	EXHAUSTION
DISEASE	LIVER DISEASES
DIETETIC DEFICIENCY	PSYCHONEUROSES AND
DISEASES	PSYCHOTHERAPY

1.—THE INCIDENCE OF GENERAL DISEASES IN TROPICAL COUNTRIES

1550.] Even in tropical countries most of the serious cases seen by the practitioner are due to general diseases of world-wide distribution. The relative incidence of the principal diseases, however, may differ widely from that prevailing in the temperate zone, and some account of the variations may conveniently be given here. The data are based mainly on an analysis by Rogers (1925) of a large number of necropsies on medical cases in Calcutta, which were in close agreement with those of the vital statistics of that city; they were compared with the data of 1,000 necropsies at St. Mary's Hospital, London. Somewhat similar figures were worked out by Megaw (1935) from returns from the Philippine Islands and from among the employees of the United Fruit Company in tropical America. The Calcutta figures showed that only one-third of the total deaths were due to tropical diseases; the remaining

*Sources of
data*

two-thirds are therefore well worthy of consideration. Calcutta has a good deep drainage system and suffers comparatively little from malarial fevers. On the other hand kala-azar, cholera, and dysenteries cause 28 per cent out of the 33 per cent of deaths due to tropical diseases.

The ages of the Calcutta necropsy subjects are very different from those in London. In order to compare the figures it is necessary to exclude cases under 10 years of age as they scarcely occur in the Calcutta data. Of the subjects above that age the percentage between 21 and 40 is 64·4 per cent in Calcutta, against only 29·4 per cent in London. As a corollary, in Calcutta only 8 per cent were over 50 and only 2 per cent over 60, compared with 38·5 and 14·4 per cent in London. The importance of this in explaining the rarity in tropical India of certain diseases of the later decades of life will appear presently, but the infrequency of enlarged prostate in Calcutta may be mentioned here.

TABLE I.—Percentages of Deaths in the Main Groups of Diseases

GROUP				LONDON	CALCUTTA
General diseases	—	—	—	6·1	9·23
Tuberculosis	—	—	—	13·4	21·93
Circulatory diseases	—	—	—	20·3	10·50
Respiratory diseases	—	—	—	16·6	27·13
Digestive diseases	—	—	—	7·5	12·00
Urinary diseases	—	—	—	8·6	6·35
Nervous diseases	—	—	—	11·9	7·41
Malignant tumours	—	—	—	13·8	4·59
Remainder	—	—	—	1·6	0·84

TABLE II.—Percentages of Deaths from the Principal Diseases

DISEASE				LONDON	CALCUTTA
General Diseases					
Anaemia	—	—	—	1·5	2·34
Leukaemia	—	—	—	1·7	0·27
Diabetes mellitus	—	—	—	0·7	0·18
Diphtheria	—	—	—	0·5	0·18
Septicaemia	—	—	—	0·5	3·00
Tetanus	—	—	—	0·1	2·05
Typhoid	—	—	—	0·3	1·21
Pulmonary tuberculosis	—	—	—	5·4	16·10
Primary intestinal tuberculosis	—	—	—	0·0	1·04
Circulatory Diseases					
Malignant endocarditis	—	—	—	2·6	1·50
Rheumatic endocarditis	—	—	—	3·7	0·00
Aortic valve disease	—	—	—	3·6	2·73
Mitral valve disease	—	—	—	4·3	0·93
Aneurysm	—	—	—	3·2	1·59

DISEASE				LONDON	CALCUTTA
Respiratory Diseases					
Lobar pneumonia	-	-	-	4.2	16.03
Broncho-pneumonia	-	-	-	6.1	5.80
Bronchitis	-	-	-	4.7	3.00
Digestive Diseases					
Gastric and duodenal ulcers	-	-	-	2.1	0.92
Enteritis	-	-	-	2.0	1.42
Hepatic cirrhosis	-	-	-	1.3	5.91
Kidney Diseases					
Parenchymatous nephritis	-	-	-	2.3	1.96
Granular kidney	-	-	-	5.4	3.46
Nervous Diseases					
Meningitis (non-tuberculous)	-	-	-	2.4	3.29
Apoplexy	-	-	-	6.2	1.96

The larger proportion classed as general diseases is due to the following *General diseases* differences in the two series. As might be expected, anaemia was the cause of death in 2.34 per cent in Calcutta as compared with 1.5 per cent in London. This is only partly due to a very few cases of ankylostomiasis. On the other hand, leukaemia was more common in London (1.7 per cent) but I have met it in Calcutta (0.27 per cent) and on one occasion was saved by a blood count from puncturing the spleen in mistake for kala-azar.

Diabetes mellitus caused 0.7 deaths in London against 0.18 in Calcutta, *Diabetes mellitus* but 0.6 per cent in the Calcutta vital statistics of persons over 5 years of age, to exclude the effect of the extremely high Calcutta infantile mortality. The disease is thus rare in the labouring classes in hospital but common in well-to-do Indians, who consume large quantities of carbohydrates and sugar. Diabetic gangrene is also frequent in such persons.

Diphtheria is somewhat less common in the tropics, although by no means rare. The deaths from this disease were 0.5 per cent in the London series, against 0.18 in the Calcutta necropsies, but 0.37 per cent in the Calcutta Health Officer's returns. *Diphtheria*

Septicaemia, including pyaemia but not puerperal fever, was the cause *Septicaemia* of 3.0 per cent of necropsies and 1.2 per cent in the vital statistics in Calcutta, against 0.5 per cent in London (for surgical necropsies are not included in the analysis). I was early struck by this fact, which is explainable on the ground that the hot moist atmosphere of Bengal is favourable to the survival of streptococci. Some of the fatal secondary infections after the old open operation for draining amoebic liver abscesses were due to post-operative streptococcal infections; they are most difficult to prevent on account of the copious discharges.

Tetanus shows the greatest difference in the two series, with 2.05 per *Tetanus* cent in the Calcutta necropsies and 1.1 per cent in the vital statistics of those over 5 years of age, against only 0.1 per cent in the London

necropsies. Still more terrible is the fact that the Calcutta health returns of 1921 showed 6.04 per cent of all deaths were due to tetanus, for infants formed 87 per cent of the total deaths from tetanus. This is due to the filthy customs of ignorant Indian midwives in dressing the umbilical cords of newly-born infants, using materials which often include the dung of the sacred cow! My attention was early drawn to the frequency of deaths from tetanus in patients admitted for street injuries in Calcutta, and experiments showed that the insertion beneath the skin of rats of a minute pinch of Calcutta street dust produced tetanus in five out of six. This led me to advocate prophylactic serum in all street wounds, and it is satisfactory to note that the incidence of tetanus in the surgical necropsies fell from 20 in the first 1,000 to 2 in the last 600. This real danger of wounds in tropical country is therefore preventable.

Enteric

Enteric fever is well known to be especially common in insanitary tropical countries. Hospital data do not bring this out fully, in spite of the London necropsies showing only 0.3 per cent of deaths from this cause against 1.21 per cent in the necropsies and 2.9 per cent in the vital statistics of Calcutta. When I first went to Calcutta in 1900 it was generally held that enteric was rare in Indians; but, although only three cases had been diagnosed as such in the previous ten years, I found six undiagnosed cases in the wards at one time by means of the Widal test, then recently introduced (Rogers, 1902). I have also seen sixteen cases at once in an European ward of twenty-four general medical beds. Indians suffer chiefly during childhood, so do not appear in the necropsy records, as they are rarely sent to hospital for enteric. The very general use of preventive inoculation against typhoid and the paratyphoids has greatly lessened the incidence of the disease in Europeans in the tropics; for the India Office and other service recruiting bodies insist on its use. The disease was greatly reduced in British soldiers in India by the isolation of all enteric patients until proved no longer to be carriers of the disease, and also by the examination of cookhouse and other servants for carriers.

Tuberculosis

It is difficult to exaggerate the importance of tuberculosis in India and other tropical countries. Yet this was late in being recognized, for in 1892 a leading Calcutta physician stated at a congress that pulmonary tuberculosis and other lung diseases were rare in natives of India. In 1904, in the course of an inquiry into the true causes of the 90 per cent of all deaths returned by the village watchman under the elastic term 'fever', I obtained clear evidence that 90 per mille of the total deaths were due to pulmonary tuberculosis. Moreover, the Calcutta necropsies show 16.10 per cent and the vital statistics 20.4 per cent due to that cause, against 5.4 per cent in the London necropsies. Further, among backward tropical races pulmonary tuberculosis is liable to take on a very acute intractable form, as pointed out by Lyle Cummins with regard to tropical Africa. In India the disease appears to be intermediate in severity between that of Europe and that of tropical Africa,

and the positive tuberculin reactions are also intermediate between the very low figures in West Africa reported by French workers and the very high rates in Europe and the U.S.A. (Rogers, 1925).

Equally interesting is the comparative rarity of surgical forms of tuberculosis in India as compared with Europe. This was clearly shown in an analysis of the admissions to the children's wards of Calcutta hospitals (Rogers). It is in accordance with the rarity of tuberculosis in cattle, 0.5 per cent in Bengal cattle living largely in the open, and nil in 200 hill cattle used in the writer's rinderpest research. On the other hand, I was struck by the frequency of primary intestinal tuberculosis in Calcutta necropsies, which were shown by inoculation experiments to be not of the bovine type. This may be related to the custom of milk being carried in open cans through the dusty streets of Calcutta, combined with free open-air expectoration of the people. *Surgical tuberculosis*

The incidence of malignant tumours in the tropics also presents points of interest. In the first place the Calcutta necropsies showed only 4.59 per cent due to this cause, against 13.8 per cent in the London series. Thus carcinomas were three times as numerous in the London series. That this is mainly due to the shorter span of life of the Calcutta subjects is clear from the fact that 76 per cent of the London cancer subjects were over 50 years of age; for it has already been stated that the subjects surviving to over that age were four times as many in London as in Calcutta. The excess of cancers in London was especially great in those of the stomach, oesophagus, and large bowel, and also of the breast. On the other hand, primary cancer of the liver formed 5.7 per cent of the Calcutta necropsies, but only 2 per cent of the London ones. *Malignant tumours*

Diseases of the circulatory system are of especial interest in view of the great rarity of true rheumatic fever in such a damp hot climate as that of Lower Bengal. Thus, in the London necropsies malignant endocarditis forms 2.6 per cent and rheumatic endocarditis 3.7 per cent of the fatal cases. In Calcutta the respective figures were 1.50 and 0.00. In Calcutta malignant endocarditis was mainly due to pneumococci. More remarkable still, among records of 4,800 necropsies spread over thirty-seven years in Calcutta only one case of typical rheumatic endocarditis was found, and that patient was not an Indian subject. Norman Chevers (1886) had previously noted the rarity of acute rheumatism in Lower Bengal. Megaw (1935), however, has met with a few cases in the hot, but less humid, north-western provinces of India. Rheumatic pericarditis is equally rare. The importance of this fact is that it alters the whole aspect of organic cardiac disease and is the main factor accounting for the proportion of deaths from circulatory diseases being twice as great in the London as in the Calcutta series. Thus, organic mitral valve disease was the cause of death in 4.3 per cent of all cases in London, but in only 0.93 per cent, less than one-fourth, in Calcutta. This is nearly all due to the great rarity of mitral stenosis in young adults or adolescents in Calcutta; although this was apparently not *Circulatory diseases*

known to some of the clinicians judging from the frequency of their having diagnosed the condition when there were no signs of it at a subsequent necropsy. On the other hand, the relative incidence of organic disease of the aortic valve only varied between 2.6 per cent in London and 2.73 in Calcutta. It was mainly atheromatous in nature, as were most of the few cases of organic mitral disease, the age incidence of which was much higher than in the London mitral cases. Aneurysms numbered 3.2 per cent in London against 1.59 in Calcutta. This is probably due to the lower blood-pressure and stamina of Indians.

On the other hand, the rare extensive and fatal atheroma throughout the pulmonary arteries, resulting in enormous hypertrophy followed by dilatation of the right heart with dropsy, is by no means unknown in Calcutta; for nine cases have been reported (Rogers, 1908), one of which was recognized in the wards. The age incidence was low and the disease was associated with gummata in some of the cases.

*Respiratory
diseases*

Respiratory diseases other than tuberculosis accounted for 27.13 per cent of the Calcutta deaths, compared with 16.13 in the London series. This is essentially due to lobar pneumonia being the commonest cause of death in Calcutta with a rate of 16.03, against 4.2 in London. The Calcutta vital statistics of those over five years of age confirm this, with a figure of 17.9 per cent. Broncho-pneumonia, however, gave the very similar figures of 5.80 and 6.1 per cent but nearly all the Calcutta cases occurred during the 1918-19 influenza epidemic; apart from this the rarity of deaths from broncho-pneumonia is a conspicuous feature of Calcutta necropsies in my long experience there. A hot climate therefore tends to increase the prevalence of lobar or pleuro-pneumonia, but to lessen that of broncho-pneumonia in hospital cases, although this is partly due to the few child subjects. The bronchitis deaths did not vary so much in the two series, and the Calcutta vital statistics show a high mortality for broncho-pneumonia and bronchitis.

*Digestive
diseases*

Diseases of the digestive system also show some interesting differences in the tropics. In this group the Calcutta deaths amounted to 12.0 per cent against 7.5 per cent in London. Gastric and duodenal ulcers, however, were more common in London, with 2.1 per cent, than in Calcutta, with 0.92 per cent. Enteritis was rarer in Calcutta, 1.42 per cent, than in London with 2.0 per cent; this is probably due to the small proportion of children in the Indian series. The most striking feature was the frequency of hepatic cirrhosis in Calcutta, 5.91 per cent, as compared with only 1.3 per cent in the London necropsies. This feature led the writer to make a special analysis of 4,800 necropsies in Calcutta to elucidate it, because the disease was frequent in Mohammedans, who are forbidden by their religion to take alcohol. It was thus found that there was one case of cirrhosis of the liver to every 3.6 cases showing dysenteric ulceration of the large intestine, mostly of a chronic form due to amoebic infection, in which repeated attacks of hepatitis occur. When liver abscess results it becomes enclosed by a dense fibrous wall, and repeated hepatitis might well result in cirrhosis of the organ. It

should also be mentioned that clinically cirrhosis of the liver may be simulated in India by ascites associated with a chronic fibroid thickening of the whole of the peritoneum. Megaw (1935) regarded this as being caused by the passage of the irritating toxins of dysentery bacilli through the bowel wall, for such a case may give agglutination with Flexner's dysentery bacillus.

Kidney diseases were rather more frequent in the London, 8·6 per cent, than in the Calcutta series with 6·35 per cent. This is mainly due to a lower proportion of cases of granular kidney, probably owing to the lower number of elderly persons. Perspiration induced by a hot climate may to some extent lessen the work of the kidney. *Renal diseases*

Fatal nervous diseases formed 11·9 per cent of the London, but only 7·41 per cent of the Calcutta series. This was solely due to the cases of apoplexy being three times as frequent in London and was doubtless also associated with the much higher proportion of subjects over the age of sixty years, and with the higher blood-pressure of Europeans on a mixed diet than that of vegetarian Hindus in India. Cases of acute meningitis were rather more numerous in Calcutta, 3·29 per cent, against 2·4 per cent in London. They were mainly pneumococcal or due to cerebrospinal fever, the latter not being rare in India. *Nervous diseases*

2.—MINOR TROPICAL DISEASES

1551.] Big heel is a painful condition met with among natives of the Gold Coast and in Formosa. It commences with fever, accompanied by pain in the heel. The os calcis becomes swollen and tender, and rarely other tarsal bones may be affected. In the course of a month or two the trouble gradually subsides, and no treatment appears to have much effect on its course. *Big heel*

Mossy foot is a papillomatous condition originally described in the Amazon River area of South America. More recently it has been met with in West Africa, Abyssinia, and East Africa. Loewenthal (1934) suggested the name lymphostatic verrucosis for the complaint. It is characterized by extensive and closely aggregated papillomas on the dorsum and spreading to the sides, but not to the sole, of the foot. They are very vascular, somewhat painful, and accompanied by some oedema of the foot and lower leg. The disease progresses very slowly, and Macfie (1936) gave the duration as from one to twenty years, and the age incidence as between ten and sixty years. No sinuses result; this enables the disease to be differentiated from Madura foot. The disease appears to be inoculable from one foot to the other, so that in time both are usually involved. Fungi have been described as occurring in the disease, but there is no consensus of opinion on its causation. Possibly more than one skin affection may be covered by the term. The cautery has been suggested for its treatment and might be effective in an early stage. *Mossy foot*

*Onalai or
chilopa*

Onalai or chilopa (bleeding disease) has been reported from Portuguese West Africa, the Belgian Congo, North Rhodesia, and British East Africa by various observers. It is a serious affection characterized by numerous umbilicated vesicles, about the size of a pea, in the mouth and nose. These contain either fluid or partly coagulated blood and are accompanied by hæmorrhages from the affected mucous membranes. The chief symptoms are bleeding from the nose and mouth, resulting in secondary anaemia and debility and often terminating in death. In fatal cases the larynx and trachea show hæmorrhages into the mucous membrane, and the stomach and oesophagus contain blood without being ulcerated. The spleen and liver are not enlarged. The disease does not appear to be infectious, although more than one case may occur in a family. No specific treatment is known. H. A. Gilkes (1934) suggested that the condition might be a deficiency disease allied to scurvy.

Chiufa

Chiufa is also reported from East Africa by H. A. Gilkes (1934) in the form of an acute inflammation beginning in the rectum and extending up to the descending colon. It is said to commence with the appearance of a white powder around the anus, and in women also on the vulva. A few days later the patient develops intermittent fever, sweating, and weakness. The skin around the anus becomes red and hard and the orifice widely patulous, exposing the inflamed mucous membrane of the rectum. There is then complete constipation, but as the inflammation spreads up to the colon vomiting, and even watery diarrhoea containing mucus, set in. Gangrene of the rectum, however, does not occur, but native patients generally succumb to the disease after three days. Neither the cause of the disease nor any effective treatment is known.

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TROPICAL GRANULOMA

See GRANULOMA, ULCERATIVE, Vol. VI, p. 54

TROPICAL LIVER

See LIVER DISEASES: TROPICAL LIVER, Vol. VIII, p. 156

TROPICAL SPRUE

See SPRUE, TROPICAL, Vol. XI, p. 419

TROPICAL ULCER

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1.—DEFINITION

(*Synonyms*.—Ulcus tropicum; phagedaenic ulcer; Naga sore; tropical ulcer; Annam ulcer; Cochin sore; Aden ulcer; Yemen ulcer)

1552.] Tropical ulcer is a rapidly spreading ulcer occurring usually on the lower extremities of the body, which quickly assumes a phagadaenic character and is accompanied by considerable pain, local oedema, sloughing, and a sero-sanguinous discharge. The edges of the ulcer are undermined and the margins are considerably raised.

2.—AETIOLOGY

Geographical distribution and epidemiology The disease occurs in endemic and sporadic forms in many tropical countries and occasionally in subtropical regions. Extensive seasonal epidemics have been described from time to time in many regions, e.g. Assam, Cochin China, Malaya, certain parts of Africa, the Solomon islands, and Melanesia. The disease is common in jungle

lands and less common in well settled areas. A high seasonal rainfall, a hot and damp climate, and marshy localities favour its occurrence.

The disease is responsible for much disability among the labour population in tea-gardens and railways, and among expeditionary forces passing through endemic regions. The resulting economic loss is at times considerable; according to Hughes the usual stay of patients in the hospital was between 141 and 232 days, and in Assam in 1926 35 to 40 per cent of the labour population in tea-gardens were at times temporarily disabled during the busiest season of the year.

Occupation plays an important aetiological part. The disease is mainly confined to the bare-footed labouring class whose occupations expose them to traumatic lesions. Children and old people are rarely attacked, and the incidence is higher in males than in females, except that it is equal in the two sexes where female labour is employed.

Much stress has been laid on the influence of debilitating conditions, such as malaria or hookworm infection. Le Dantec (1899) found that tropical ulcer had the same geographical distribution as malaria; Cross regarded it as a manifestation of malaria and termed it malaria ulcer. According to Plehn it is a disease of poverty and misery, but Strong disputed the statement that the clinical course of ulcers was adversely affected by the constitution of the natives. Patterson (1908), with a very wide experience of a large epidemic in tea-gardens in Assam, was convinced that malaria, kala-azar, hookworm, starvation, and debilitating conditions due to other causes did not influence the disease.

Edge classed the condition as a deficiency disease; Young, on the other hand, considered that the evidence for dietary deficiency, put forward by Orr and Gilks and by McCulloch, was by no means convincing. Byron found the blood calcium in eighty-four Chinese suffering from ulcers to vary between 8.4 and 9.5 per 100 c.c. but administration of either calcium, cod-liver oil, or mammalian liver raw or semi-cooked (Hughes, 1931) had not any beneficial effect on the progress of the ulcers. I had the same experience in Assam. Improvement of diet and treatment of coexistent pathological conditions do not influence the course of the disease, so that malnutrition from various causes, as commonly evident among such labouring population, cannot be seriously considered as the chief predisposing cause.

The ulcer starts in a trauma, i.e. any breach of the skin, such as injuries, pricks, cuts, insect and animal bites, ankylostoma papules, and irritation caused by poisonous plants. It is assumed that secondary infection, the nature of which is unknown, supervenes on the primary traumatic lesion. Spirochaetes and Vincent's bacilli have been regarded as causal agents merely because of their presence in a large proportion of the ulcers and their penetration deep into the tissues, but without due consideration that they may be merely saprophytes.

Occupation

*Age and sex
incidence*

*Relation to
parasitic
infestation
and debility*

Diet

Trauma

3.—BACTERIOLOGY AND MORBID ANATOMY

*Organisms
isolated from
lesions*

Le Dantec claimed to have been the first in 1884 to find a bacillus, Vincent's bacillus, in French Guiana, and Plaut (1894) first drew attention to the presence of a fusiform bacillus, commonly associated with a spirillum, in ulcerative lesions of the mouth, throat, and pharynx. Vincent (1896) described fusiform bacilli associated with a spirillum from the ulcers of forty out of forty-seven Arabian tourists who had returned from Madagascar; he detected the same organisms in noma, Plaut-Vincent's angina, scurvy, and hospital gangrene, and was convinced of the pathogenicity of these organisms. In 1905 Blanchard described and named this spirochaete after Vincent, and Prowazek in 1907 gave

it Schaudinn's name; both attributed these ulcers to the spirochaete. The consensus of opinion is that *Trep. vincenti* and *S. schaudinni* are identical. The pathogenicity of these organisms has been emphasized by numerous observers (Vincent; Blanchard; Wolbach and Todd; Keysseltz and Mayer; and Smith). They are indistinguishable from the organisms obtained in gangrenous ulcers, noma, syphilitic sores, gangrene and abscess of the lungs, and bronchial spirochaetosis.

The pleomorphic nature of spirochaete and fusiform bacilli has long been recognized. *S. schaudinni*



FIG. 11.—Fusiform bacilli and spirochaetes in direct smear from tropical ulcer: Giemsa (This and Fig. 12 from *Indian Medical Gazette*, 1928)

*Cultivation
of spirochaete
and fusiform
bacilli*

varies in length from 6 to 22 μ . Weaver and Tunnicliff were the first to cultivate them successfully. David Semple and his co-workers (1919) declared that in cultures the two organisms are indistinguishable. Smith (1933) followed the method adopted by Krumwiede and Pratt (1913) with consistent results. Vincent's bacilli in cultures show well marked motility. Both spirochaete and Vincent's bacilli can be recognized quickly in smears taken from the discharge and stained with Leishman's or Giemsa's stains (see Fig. 11).

*Other
organisms*

In addition to the spirochaete and fusiform bacilli, bacteria and cocci have been described.

*Histo-
pathology*

Exhaustive histopathological studies have been made by Strong; Sanarelli; Keysseltz and Mayer; and Wolbach and Todd. The upper layer of the ulcer shows a dense homogeneous layer in which the structure of the tissue can no longer be recognized. Scattered here and there are clusters of red blood-cells and polymorphonuclear leucocytes and in places much fibrin can be detected. A little deeper the number

of leucocytes is greatly increased and a dense coagulation of liquid exudate also takes place; the process represents an extensive coagulation-necrosis. Deeper still there is a great proliferation of connective-tissue cells. According to Smith (1930), sections from actively progressing ulcers of from 2 to 4 weeks' duration show the spirochaete invading to a considerable extent the granulation tissue at the base of the ulcer. The Malpighian layer of the epithelium in the neighbourhood of the ulcer margin is, as a rule, densely infiltrated by the spirochaete. The fusiform bacilli, on the contrary, remain for the most part superficial, forming a dense 'pallisade' or fence-like barrier just below the surface of the ulcer, but covered more or less completely by a layer of necrotic material heavily infected with organisms of various kinds. The 'pallisade' of fusiform bacilli stops short of the epithelial borders of the lesion. The bacilli forming the pallisade are arranged in closely packed perpendicular masses. The presence of spirochaetes in the walls of small vessels within the capillary is, according to Smith, an additional proof of the invasive tendency of these organisms and he suggested that they might be present in the blood-stream.

Although Le Dantec, Apostolides, Patterson, Fox, and Hall Wright *Inoculation experiments*

claim to have successfully transferred the disease to both men and animals, the bulk of opinion is against such a view. Lloyd Patterson first suggested that the eye-fly *Siphonella funicola*, Meij (see Vol. II, *Eye-flies*

p. 127), which has a close seasonal coincidence with tropical ulcerations, was responsible for the spread of the disease. This view was further strengthened by Wright's experiment on himself in 1919. On the other hand, I was able to prove in Assam that these flies are incapable of converting experimental scratches or abrasions into typical phagedaenic conditions and that they cannot play a prominent part in the outbreak of an epidemic, although the advent of the eye-fly and that of Naga sore are simultaneous. Fox reported that in one tea-garden fourteen coolies, when inoculated with cholera vaccine, developed Naga sore on the site of the puncture. Another author reported the occurrence of the disease on unhealed vaccination sores, and Blanchard also reported tropical phagedaena supervening on vaccine pustules.

Infection of inoculation punctures

4.-CLINICAL PICTURE

The parts of the body naturally subjected to trauma are mostly *Site of origin* affected; hence the ulcer commonly occurs below the knee. The starting point of the ulcer is always a cut, abrasion, insect bite, or other traumatic lesion.

The ulcer may be single or multiple. The site of injury soon turns into an ulcer, which spreads rapidly, deepens considerably, and becomes covered with a greyish-yellow thick purulent foul-smelling slough. The margins tend to become undermined from the beginning. The spread in some cases is so rapid that in the course of five to eight days *Ulceration*

it presents a phagedaenic appearance with fetid discharge. The superficial fascia, muscles, tendons, nerves, and vessels may be destroyed. In severe cases necrosis of bone may take place. The shape depends on the nature of the injury (see Fig. 12): a prick results in a circular ulcer and a cut from a spade in an irregular form. Considerable swelling of the affected part is frequent and may even simulate filarial elephantiasis. The margins of the ulcers are considerably raised and present a cup-shaped appearance when the ulcer is circular. It is difficult to make out its depth on account of the presence of a tenacious slough;



Pain and constitutional symptoms

FIG. 12.—Tropical ulcer

it contains numerous spirochaetes and fusiform bacilli. A watery sero-sanguineous discharge from the ulcer is extremely putrid and has a gangrenous odour. The slough is so adherent that it is difficult to remove it and the underlying red granulation-tissue bleeds on the slightest attempt at removal.

Patterson and Scott laid stress on pain as an important symptom. Scott remarked, 'I have in mind a clear picture of the unfortunate

patients sitting on the hospital verandah nursing their legs and displaying in their faces the utmost misery and pain, they would not have the sores touched and suffered greatly when they were dressed'. Walking and standing are very painful, but the pain is considerably relieved by lying down. Enlargement of neighbouring glands is infrequent. There is little or no constitutional disturbance. The disease is generally non-febrile during its whole course.

These ulcers are generally self-limited and the majority do not extend beyond the deep fascia. Healing is very slow and leaves a whitish scar which is sometimes disfiguring. No immunity, local or general, is conferred.

5.—DIAGNOSIS

Diagnosis must be made by the general appearance of the ulcer and its phagedaenic character. Veldt sore (see p. 538) is a different condition.

6.—TREATMENT

In order to prevent cuts and abrasions I first suggested the wearing of puttees, and Kerby stated that the incidence of *ulcus tropicum* has decreased enormously wherever the wearing of puttees has been enforced. *Prophylaxis*

There is a wide divergence of opinion as to the efficacy of any particular method of treatment. Treatment should be mainly in accord with surgical principles and local. Attention should, however, be paid to the patients' general health and hygiene, and dietary deficiency should be corrected, although improvement of the diet does not materially shorten the course of the disease. Absolute rest is essential and should be the fundamental part of the treatment. *General treatment*

An essential preliminary is the cleansing of the surface of the ulcers by powerful caustics such as pure liquefied phenol or copper sulphate. McGuire stated that an ulcer of the usual size healed in about two weeks under the following treatment: swabbing of the ulcer twice daily with a solution containing copper sulphate 180 grains, phenol 60 grains, distilled water 1 fluid ounce, followed by dusting with a powder consisting of one part of iodoform and three parts of bismuth subgallate. This treatment is painless. Bathing the affected parts in a disinfectant lotion such as solution of mercuric chloride, potassium permanganate, eusol, or electrolytic chlorogen, followed by the application of iodoform and boric acid, is generally recommended. *Local: cautery*
Antiseptics

Chronic ulcers may show a poor tendency to heal; their undermined and indurated edges should be clipped away with scissors followed by application of B.I.P.P. When the ulcer spreads in spite of the most energetic treatment, its total excision under local or general anaesthesia should be tried. Healing is hastened by Thiersch skin grafting. *Scraping and excision*

Sayers modified Dickson Wright's method of strapping to the treatment of *ulcus tropicum*. The leg is firmly encased from foot to knee in a 3-inch spiral bandage; no special attention is paid to discharge from the ulcer, and the bandage is changed once a week. The patient is allowed to continue his usual activities. *Strapping*

Arsenical preparations, and dyes, such as methyl violet, brilliant green, and acriflavine, have not proved effective, and X-ray therapy is disappointing. Loewenthal reported that daily intravenous injections of 15 grains of calcium chloride in 10 c.c. of distilled water, until recovery was complete, promoted rapid separation of the slough and healing of the ulcer. Brown obtained excellent results from parathyroid treatment. Maggot treatment may prove useful and may be given a trial (see MYIASIS, Vol. IX, p. 64). *Drugs and X-rays*
Calcium and parathyroid
Maggots

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TRYPANOSOMIASIS

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Reference may also be made to the following title:

ARTHROPODS AND DISEASE

1.—DEFINITION

(*Synonym.*—African trypanosomiasis)

1553.] Sleeping sickness is an infection met with in tropical Africa due to protozoal parasites belonging to the genus *Trypanosoma*, disseminated by various tsetse flies (*Glossina*), and characterized by irregular febrile

disturbances, by an erythematous eruption and localized oedemas, by a polyadenitis, tachycardia, and later in the disease by various nervous phenomena; in untreated cases the infection usually terminates in coma and death.

2.-PARASITOLOGY

(1)—Trypanosomes

Trypanosoma
gambiense
and *T.*
rhodesiense

Two forms of sleeping sickness are commonly recognized, one due to *Trypanosoma gambiense* and the other to *Trypanosoma rhodesiense*. Although the identity of these two trypanosomes has been the subject of much discussion, and considerable evidence has been accumulated indicating that they are very closely related if not identical, nevertheless from the clinical point of view it is convenient to regard the parasites, and the diseases which they cause, as separate entities. Their geographical distributions are not the same, the tsetse flies responsible for their dissemination differ, the two infections exhibit certain clinical differences, and their reactions to drugs differ.

Trypanosoma gambiense and *T. rhodesiense* are found in the blood usually in scanty numbers, but sometimes, especially in the case of

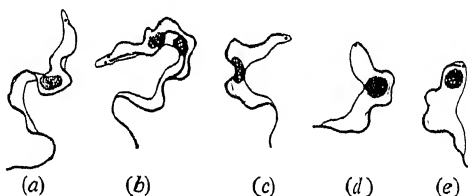


FIG. 13.—(a)-(d), various forms of *Trypanosoma gambiense* and *T. rhodesiense* met with in human blood, and (e) the posterior-nuclear forms found in the blood of animals inoculated with *T. rhodesiense*. $\times 1300$

Morphology

T. rhodesiense, they may be present in large numbers. They belong to the polymorphic group of trypanosomes and are curved fusiform organisms varying from about 10 to 12μ up to 32μ in length. The shorter individuals are relatively broad but the longer forms are slender. The nucleus is large and is situated towards the centre of the body, and the kinetoplast is small and near the posterior end. From the kinetoplast arises a flagellum which runs anteriorly and is bound to the body by a delicate undulating membrane. In the long and slender individuals the flagellum is continued some distance beyond the anterior end of the body as a free flagellum; in the short and broad forms the flagellum ends at, or immediately beyond, the anterior end of the body, so that the free flagellum is either absent or extremely short. The parasites multiply in the blood-stream by longitudinal division (see Fig. 13, a to d). In cover-slip preparations of fresh blood, the trypanosomes can readily be detected owing to their motility; they wriggle actively *in situ* creating a disturbance among the red corpuscles.

Motility

In the blood of man the two trypanosomes are morphologically indistinguishable from one another. When they are inoculated from

man into small laboratory animals, e.g. rats, mice, and guinea-pigs, *T. rhodesiense* is much more pathogenic than *T. gambiense*. *T. rhodesiense* produces a rapidly fatal disease in these animals and the trypanosomes are found in larger numbers in the peripheral blood. Certain of the short broad trypanosomes in the blood of laboratory animals infected with *T. rhodesiense* exhibit a morphological peculiarity, the nucleus being displaced posteriorly (see Fig. 13, e) and in extreme cases lying actually between the kinetoplast and the posterior extremity of the body. Such forms are termed posterior-nuclear forms: they are believed to be due to irregular division, and although they are common in *rhodesiense* infections of laboratory animals, sometimes constituting 5 per cent or more of the total short forms, they have very rarely been seen in *gambiense* infections.

*Relative
pathogenicity
for laboratory
animals*

(2)—Vectors

Although it has been proved experimentally that many of the tsetse flies are capable of transmitting both *T. gambiense* and *T. rhodesiense*, nevertheless in nature *Glossina palpalis*, and to a less extent *G. tachinoides*, are chiefly responsible for the dissemination of *T. gambiense*, and *G. morsitans* and *G. swynnertoni* for that of *T. rhodesiense*.

Glossina are narrow-bodied and elongate, dark brown, blackish, yellowish-brown, or yellow flies ranging in size from about 8 mm. to 13 mm. according to the species. They are recognizable when alive and at rest by their wings being closed flat one over the other like the blades of a pair of scissors, and by the biting proboscis projecting horizontally in front of the head (see Fig. 14). Both sexes

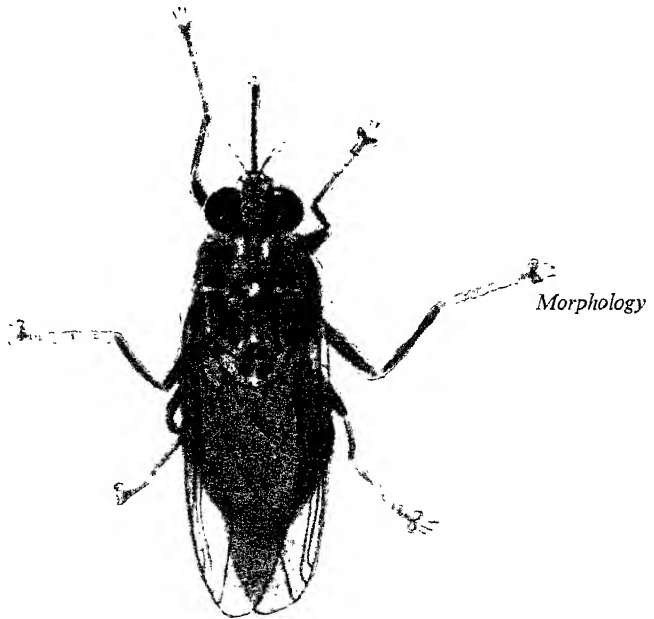


FIG. 14.—*Glossina morsitans*, dorsal view: $\times 4\frac{1}{2}$ approx. (This and Fig. 15 from *Guide to the Study of Tsetse-Flies* by R. Newstead)

are blood-suckers and feed during the daytime.

The female gives birth to a single larva at intervals of several days. The larva is a creamy-white or pale yellow footless maggot, nearly as large as the abdomen of the mother, with a pair of intensely black shining protuberances at the posterior end, separated by a depression

Life history

containing the respiratory apertures. The larvae immediately after birth crawl to a place of concealment and quickly pupate. Tsetse fly pupae are dark brown, and the tumid lips seen in the larva are equally conspicuous in the pupa (see Fig. 15). The pupa hatches within three to five weeks according to the climatic conditions, and the adult fly emerges.

Geographical
distribution

For all practical purposes the geographical distribution of *Glossina* is confined to the tropical and subtropical portions of the African continent. Within this area tsetse flies are not found continuously but are

Habitats

restricted to 'belts' or 'patches' of forest and bush. The various species differ in their habitats: *Glossina palpalis* and *G. tachinoides* are never found far from water-courses, whereas *G. morsitans* and *G. swynnertonii* are widely distributed independently of water.



Transmission
of infection

(3)—Trypanosomal Cycle in Tsetse Fly

Glossina owes its importance in the dissemination of sleeping sickness to the fact that the trypanosomes undergo a definite and complicated biological development in its digestive system, the anatomy of which is shown in Fig. 16. It has been shown that a tsetse fly can transmit the infection mechanically when it is removed from an infected animal before it has completed its meal and

FIG. 15.—Pupa of *Glossina morsitans*: $\times 7\frac{1}{2}$

transferred immediately to a healthy animal, but there is little doubt that transmission of the infection from man to man by this method of interrupted feeding is exceptional in nature. When, however, such flies are subsequently fed on a succession of healthy animals, they do not transmit the infection until after the lapse of a period which varies with the temperature, and possibly with other conditions not yet understood, and which is usually from about ten to twenty-five days. During this latent period the trypanosomes are undergoing their biological cycle of development in the fly, the main features of which are as follows.

Latent
periods

Trypanosomes
in gut

In the infecting meal the trypanosomes are carried with the blood into the intestine of the fly. Here they multiply and change morphologically, becoming large and broad (see Fig. 17, *a*), and lose their capacity for infecting the vertebrate host. Within a few days they pass round the posterior end of the peritrophic membrane to reach the extra-peritrophic space situated between the membrane and the epithelial cells lining the intestine. The peritrophic membrane is a delicate sleeve-like membrane which is secreted by certain large cells in the proventriculus and extends down the intestine about as far as the entry of the Malpighian tubes; it thus separates the epithelial cells of the intestine from the intestinal contents (see Fig. 16, *B*). In the extra-peritrophic space the trypanosomes multiply enormously and undergo

In extra-
peritrophic
space

further changes in morphology. About the tenth day the swarm of trypanosomes has extended anteriorly along the extra-peritrophic space and reached the level of the proventriculus. They then escape from the extra-peritrophic space at the place where the membrane is formed and reach the lumen of the proventriculus. The trypanosomes found in the *In proventriculus*

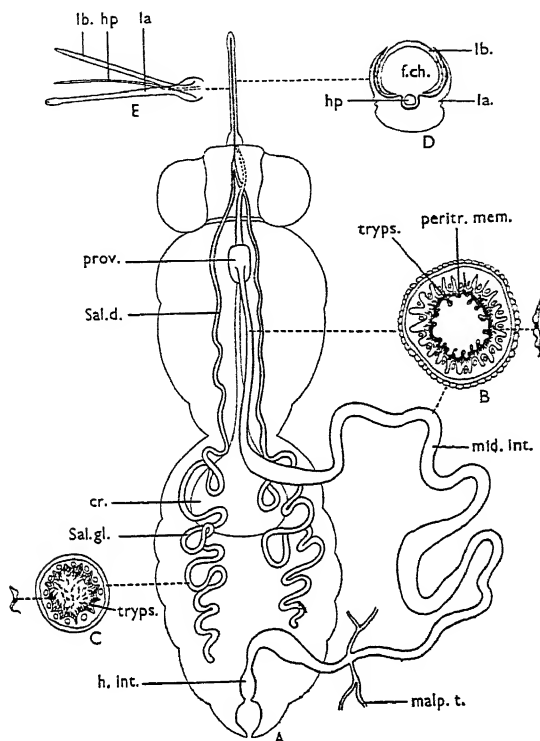


FIG. 16.—Diagrammatic representation of: A, internal anatomy of *Glossina*; B, transverse section of mid-intestine, showing trypanosomes between peritrophic membrane and epithelial cells lining intestine; C, transverse section of infected salivary gland; D, transverse section through proboscis; and E, longitudinal view of proboscis. *cr.*, crop; *f. ch.*, food channel; *h. int.*, hind intestine; *hp.*, hypopharynx; *la.*, labium; *lb.*, labrum-epipharynx; *malp. t.*, Malpighian tubes; *mid. int.*, mid intestine; *peritr. mem.*, peritrophic membrane; *prov.*, proventriculus; *sal. d.*, salivary duct; *sal. gl.*, salivary gland; *tryps.*, trypanosomes

proventriculus are very long and slender and characteristic (see Fig. 17, *b*). The parasites maintain themselves in the proventriculus partly by multiplication of the long slender forms and partly by continual replenishment from the trypanosomes multiplying in the extra-peritrophic space. The infection spreads forward from the proventriculus up the oesophagus along the labial cavity in the proboscis, back into the hypopharynx, and so into the ducts of the salivary glands and finally into the glands. When the long slender trypanosomes of the proventricular type reach the salivary secretion they change into *In salivary glands* crithidia and then, after active multiplication, into trypanosomes closely

resembling those found in the blood of man (see Fig. 17, *c* and *d*). These last forms, which are known as metacyclic trypanosomes, are capable of infecting the vertebrate host and represent the completion of the developmental cycle in the tsetse.

Infective forms

Factors influencing transmission

Temperature

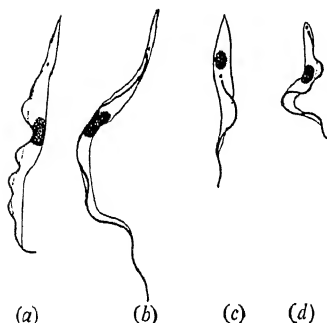


FIG. 17.—Developmental forms of *T. gambiense* or *T. rhodesiense*. (a) gut form; (b) proventriculus form; (c) crithidial form from salivary glands; (d) metacyclic form from salivary glands. $\times 1300$

In comparatively few of the tsetse flies which feed on an infected man or animal do the trypanosomes succeed in completing their complicated evolution. The factors determining the proportion of flies which become infective are as yet obscure. Climatic conditions, especially temperature, exert an important influence. As long ago as 1912, Kinghorn and Yorke showed that relatively high temperatures (75°–85° F.) were necessary for the completion of the developmental cycle of *T. rhodesiense* in *G. morsitans*. It is known that trypanosomes in the blood

of some patients and of some animals are much more capable of developing in the tsetse than are those in other patients or other animals. Furthermore, it has been established by Van Hoof, Henrard, and Peel (1937) that newly hatched flies which make their first meal on an infected man or animal are more likely to become infected than are those which have one or more feeds on a normal animal before the infecting meal. Flies in which the trypanosomes have completed their developmental cycle remain infective indefinitely.

Age of flies

Duration of infectivity

3.—GEOGRAPHICAL DISTRIBUTION

T. gambiense

Sleeping sickness is widely distributed in tropical Africa between latitudes 15° N. and 20° S. Broadly speaking, the form of sleeping sickness due to *Trypanosoma gambiense* is found in West and Equatorial Africa and does not extend eastwards beyond the littorals of the great lakes. Cases have been found as far north as Senegal and the Anglo-Egyptian Sudan, and as far south as Angola and Bechuanaland. In many parts of this vast area the disease is either absent or only mildly endemic but in other places it occurs in great epidemics. The most severely affected zones are found in the basins of the great rivers and their tributaries, namely the Gambia river, the Volta, the Niger, and above all the Congo. This is because the chief vector of *gambiense* sleeping sickness is *Glossina palpalis* which is strictly limited in its distribution to water-courses and is never found far from the banks of rivers or the shores of lakes.

High incidence in river valleys

T. rhodesiense

The form due to *Trypanosoma rhodesiense* occurs chiefly in south-east

Central Africa, i.e. in Northern Rhodesia, Nyasaland, Tanganyika, and Portuguese East Africa. In most of these countries the disease occurs sporadically and not in epidemic form, but epidemic foci exist in Tanganyika. The chief vectors of this form of the disease are *G. morsitans* and *G. swynnertoni* which, unlike *G. palpalis*, are not limited in their distribution to water-courses.

In 1936 Deutschman stated that in the African territories situated between the tropics, the total population of which may be estimated at 65 millions, nearly 7 millions were examined for sleeping sickness in the course of a year (1934-35), and 140,000 fresh cases of the disease were discovered and treated, besides a similar number of old cases.

Number of cases

4.—MORBID ANATOMY

(1)—Morbid Changes in Tissues

In many patients the trypanosomes multiplying in the skin at the site of the infective bite produce an indurated inflammatory lesion which subsides without suppuration. Within a very short period the trypanosomes invade the blood-stream, where they multiply and give rise to a general septicaemia. Although there is good reason to believe that many of the organs of the body, such as the liver, spleen, kidneys, heart muscle, the minute blood-vessels, and haemopoietic tissue, are damaged by the toxins secreted by the trypanosomes, the chief reactions are seen in the lymphatic glands and in the leptomeninges. There is a general adenitis, the lymphatic glands becoming enlarged and elastic. In section they show a hyperplasia of the follicles and a multiplication of the macrophages in the sinuses, and around the vessels is an infiltration of leucocytes and plasma cells. Later the glands become sclerosed, the follicles and glandular tissue being replaced by fibrous tissue.

Skin lesion

Invasion of blood-stream

Lymph glands

The most important changes in sleeping sickness occur in the pia-arachnoid. The minute blood-vessels in the meninges, in the choroid plexuses, and in the brain substance are damaged by the trypanosomes, which eventually pass through the altered endothelium into the perivascular spaces and give rise to a leptomeningitis. This inflammation of the leptomeninges is precocious and progressive and is responsible for the characteristic clinical manifestations of the disease.

Lepto-meningitis

At necropsy the dura mater, in advanced cases, is adherent to the cranium and to the underlying meninges. On incising the dura a considerable amount of clear fluid may escape, and the brain appears oedematous and congested. In such cases, owing to the intracranial pressure, the surface of the brain is smooth; the sulci tend to be obliterated but the convolutions are broad and of normal size. In less pronounced cases there is little excess of fluid and the surface of the brain appears normal. The meningitis is predominantly vertical and according to Calwell rarely extends more than half-way down the sides of the cerebral hemispheres. Meningeal adhesions at the base of

Post-mortem appearances

the brain are rare. There is a diffuse generalized leptomeningitis, which is just as marked on the inner surface of the hemispheres as on their lateral aspects. The brain is of normal consistence, but here and there it may exhibit softenings at the sites of haemorrhagic foci. The ventricles are often distended, and the choroid plexuses show signs of chronic inflammation.

Histology

On microscopic examination the generalized leptomeningitis is manifested not only by a proliferation of the neuroglia cells in the adjacent nervous substance but also by a proliferation of the endothelial cell nuclei and by infiltration of the pia-arachnoid with lymphocytes and plasma cells.

Perivascular infiltration

A striking feature of sections of the brain is a universal perivascular infiltration. This consists of a proliferation of the vascular endothelium,

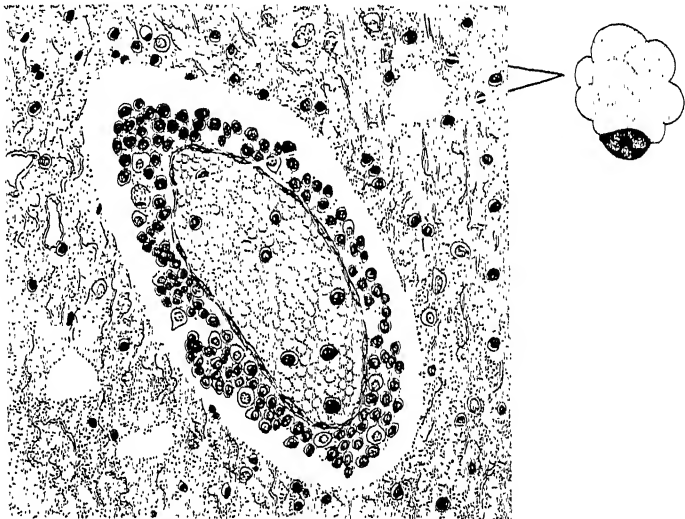


FIG. 18.—Section of brain showing perivascular infiltration ($\times 280$), and morular cell ($\times 1300$)

and packing of the Virchow-Robin space—the continuation of the subarachnoid space formed by the reflection of the pia-mater along each blood-vessel which enters the nervous tissue—with proliferated and enlarged neuroglia cells, and with lymphocytes, plasma cells, and morular cells (see Fig. 18). Morular cells, which were first described by Mott, are large round or oval cells with the nucleus staining deeply blue and pushed to one end or pole; the cytoplasm contains a large number of clear spherules staining with eosin and giving the cell a mulberry appearance. The origin of these peculiar cells is still uncertain; Mott, who found them also in infected lymphatic glands, believed that they were degenerate plasma cells. Peruzzi concluded that, although probably they had a multiple origin, the neuroglia was their most common source. Mackie found morular cells most common in the cellular exudate of the pia-mater and Virchow-Robin spaces; but, as

Morular cells

he also found them in normal intestinal mucosa, he agreed with Mott that their origin cannot invariably be neuroglia cells. Bertrand, Bablet, and Sicé are of opinion that they are derived exclusively from plasma-cytes.

Chronic inflammatory change in the central nervous system is manifested by proliferation and overgrowth of the neuroglia cells, especially those related to the subarachnoid and perivascular spaces. The lesions of the neural elements are, as a rule, slight and not comparable with those seen in general paralysis. In sleeping sickness the morbid change is thus primarily interstitial, with some secondary parenchymatous atrophy. *Inflammatory changes*

(2)—Changes in Cerebrospinal Fluid

During the course of sleeping sickness certain very characteristic changes occur in the cerebrospinal fluid. According to Sicé, the alternating multiplication of trypanosomes in the general circulation, and their subsequent destruction during the trypanolytic crises, which are a constant feature of the evolution of the disease, occasion vascular changes which are particularly manifest in the region of the terminal ramifications of the blood-vessels. The choroidal plexuses of the ventricles, which are in the main responsible for the secretion of the cerebrospinal fluid, consist essentially of numerous large convoluted capillaries embedded in loose connective-tissue covered by a layer of specialized epithelium, and appear to be very vulnerable. These plexuses, however, are not the only source of cerebrospinal fluid: it also receives contributions from the Virchow-Robin spaces, which surround the blood-vessels nourishing the brain substance and open into the subarachnoid space. The cerebrospinal fluid is thus formed at the surface and in the depth of the brain and passes from one part to another through the foramina of Magendie and Luschka (see Fig. 19). Thus the morbid changes which occur in the choroid plexuses, in the Virchow-Robin spaces, and in the pia-arachnoid are manifested by the changes in the cerebrospinal fluid. For details of the formation and circulation of the cerebrospinal fluid see Vol. III, p. 55.

The cerebrospinal fluid is usually clear; exceptionally, when the cellular reaction is very great, it may be opalescent, but in such cases it is well to consider the possibility of bacterial infection. Usually the pressure is slightly raised, 30 to 35 cm. of water in the sitting position, but sometimes it may reach as much as 100 cm. of water; subnormal pressure is exceptional. *Physical changes*
Pressure

An increase in the number of white cells is the earliest change seen. At first there is a simple increase in the lymphocytes which, instead of being 2 or less as in the normal state, are found to be 10 to 20 or more per c.mm. As the disease progresses the number of lymphocytes increases, and other cells, namely plasma cells, morular cells, large mononuclear cells, and occasional eosinophil cells, indicative of more pronounced changes, appear, so that in advanced cases the total cells *Cytological changes*

Trypanosomes
in spinal
fluid
Chemical
changes

in the cerebrospinal fluid may number several hundreds and even thousands per cubic millimetre. Trypanosomes are often, but by no means invariably, found in the centrifugalized deposit.

Increase in the total protein content is a very important and constant sign: instead of the normal amount of about 0.2 gram per litre, the

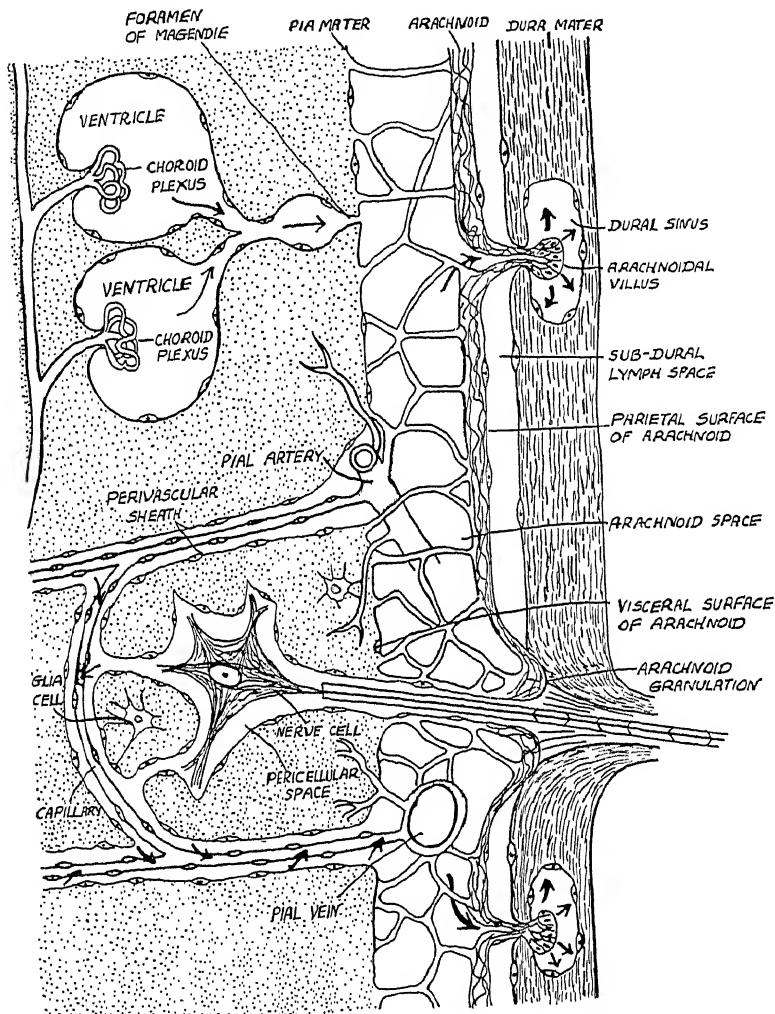


FIG. 19.—Diagram showing circulation of cerebrospinal fluid
(From *The Diagnosis of Nervous Diseases* by Purves Stewart)

value may be from 0.3 gram up to 1.0 gram or even more. Coincidentally, with increase in protein there is a fall in the chloride and sugar values.

Colloidal reactions, particularly the modification of Lange, have been examined repeatedly in human trypanosomiasis by Le Dentu and Vaucel, and by Fairbairn, and others. Fairbairn tested the cerebrospinal fluid of a number of *rhodesiense* sleeping sickness patients with Lange's

*Colloidal
reactions*

colloidal gold reaction and also estimated the total proteins present. He found that the reaction was usually of the 'tabetic' type, the intensity running parallel with the amount of protein present; when the reaction was of the 'general paralysis' type it had a grave prognostic significance.

Fairbairn considered that estimation of the total protein is the best guide to prognosis; it is also the best evidence in deciding when a patient is cured, and whether the case is one of relapse or reinfection. The colloidal gold reaction is influenced by treatment earlier than is the amount of protein and is consequently not so useful in prognosis.

The first change produced in the cerebrospinal fluid by meningeal inflammation is, then, a cellular reaction. The number of lymphocytes and mononuclear cells increases, as a rule slowly; living cells indicate an active inflammatory process, but the appearance of dead cells suggests old chronic lesions. Broden considered that the presence of vacuolated cells and morular cells in the cerebrospinal fluid implied old-standing and grave involvement of the central nervous system.

As the cellular reaction develops, the amount of protein in the cerebrospinal fluid increases. The increase is, as a rule, gradual but may continue until the amount reaches 1 gram or more per litre. According to Sicé this is a certain sign of inflammatory changes, not only in the meninges but also in the parenchyma. In some cases the increase of protein stops for prolonged periods, and this seems to indicate an arrest in the evolution of the disease. In short, the number of cells, which is an indication of the degree of meningeal vascularity, may fluctuate rapidly; but the excess of protein, which is an indication of profound lesions involving the parenchyma, varies much more slowly: it often falls to a level of about 0.4 gram per litre and remains there indefinitely.

Usually, when the patient exhibits definite nervous symptoms, changes can be seen in the cerebrospinal fluid; the reverse, however, is not true, because it is now known that the cerebrospinal fluid may exhibit morbid changes in cases which do not present any clinical signs of nervous lesions. For example, Bertrand, in 601 lumbar punctures in sleeping sickness regions, found changes in the spinal fluid in 34 per cent of the infected cases which showed no clinical signs. De Marqueissac found a cellular reaction in the spinal fluid of 46.5 per cent of patients who were clinically in good general condition, and somewhat similar observations have been made by other investigators.

In human trypanosomiasis the nervous system becomes involved much earlier in the disease than was formerly thought. Among Europeans, in whom the approximate date of infection is easier to ascertain than in African patients, Sicé discovered morbid changes in the cerebrospinal fluid of three cases with *gambiense* sleeping sickness four, eight, and ten months, respectively, after infection; and Leger recorded early changes in the cerebrospinal fluid of three Europeans infected in the Ivory Coast. Buchanan discovered a pronounced cellular reaction in the spinal fluid of ten patients suffering from *rhodesiense* sleeping sickness within three months of the first clinical manifestations of the

*Use of tests
in prognosis*

*Earliest
change*

*Later
changes*

*Relation of
changes in
cerebrospinal
fluid to
clinical signs*

*Time of
appearance
of changes
in fluid*

disease. Observations by Keevill and by Maclean and Fairbairn also indicate that in *rhodesiense* infections the cerebrospinal fluid may exhibit changes very soon after a person becomes infected.

5.—CLINICAL PICTURE AND COURSE

*Trypanosomal
chancre*

It has recently become recognized that in many patients the first sign of the disease is a local lesion at the site of the infective bite. This primary lesion is a furuncle-like swelling of the skin, which does not produce pus, and which appears within a few days of the bite of an infected *Glossina*. In well marked cases the trypanosomal chancre, as it is called, consists of a raised, indurated, button-like area, dark red or violet-red in colour and measuring up to 3 or 4 cm. or even more in diameter. The surrounding tissue is oedematous and the lesion is painful and very sensitive to pressure; it may persist for two or three weeks. That these lesions are due to the trypanosome, and not to inflammation resulting from the bite or to secondary infection, is proved by the presence of large numbers of trypanosomes in the tissue fluid, and by the fact that the lesion is quickly cured by trypanocidal drugs. Although in pronounced cases the lesion is very characteristic, in many cases it is less definite and forms a small bluish-red, indurated, slightly raised area, which can be distinguished from a non-infective bite because it is harder, more sharply demarcated, and persists for some days. According to Graf well marked trypanosomal chancres are always associated with severe general symptoms; when the primary lesion is but slightly developed the general symptoms are mild.

Although until recently this trypanosomal chancre has received little attention, during the last few years it has been reported from many quarters. It has been seen both in *T. gambiense* and *T. rhodesiense* cases, and although there seems no doubt that it may be absent in a certain proportion of cases it is probably exhibited by the average European case. The recognition of these trypanosome chancres is important from the point of view of early diagnosis, because trypanosomes can be found in them in considerable numbers some days before they can be discovered in the blood.

Onset

Seven to fourteen days after the infective bite the infection manifests itself suddenly by a sharp febrile disturbance, which is often associated with a rigor. The temperature rises quickly and within a day or two may reach 103° or 104° F. At this time trypanosomes are usually present in the peripheral blood in sufficient numbers to be discovered by microscopic examination. After about a week the temperature often falls to normal for a few days and then rises again. The second febrile disturbance is usually less violent than the first and of shorter duration. This fever of invasion, as it is called, is characterized by violence, tendency to remit and to recur, and gradual subsidence.

Pyrexia

*Fever of
invasion*

When the initial acute febrile disturbance is over, the patient passes

into a non-febrile state or, more commonly, into a state in which the morning temperature is normal and the evening temperature slightly raised to 99° or 99.5° F. At irregular periods this condition of comparative non-febrile calm is interrupted by acute exacerbations of fever lasting a few days. *Non-febrile stage*

Asthenia, which is so characteristic of the disease, appears early and becomes progressively more pronounced. Headache, at first transitory but later permanent, is constant. The patient becomes drowsy during the day but suffers from insomnia at night. Other important early signs of the disease are a generalized adenitis, tachycardia, erythematous eruptions, and localized oedemas. *Asthenia*

Enlargement of the lymphatic glands is one of the earliest and most characteristic signs, the importance of which in diagnosis was emphasized in 1906 by Dutton and Todd. The hypertrophied glands are easily felt; they are freely movable and are, as a rule, painless; they are elastic and semi-fluctuating, giving the sensation of a ripe damson on palpation. In this stage the glands are characteristic of the disease, and from them the trypanosomes can be readily obtained on puncture (see p. 278). Later the glands become sclerosed and are



*Enlargement
of lymphatic
glands*

FIG. 20.—Early case of sleeping sickness, the main symptoms being severe and continued headache and inability to sleep at night. (This and Fig. 21 from *Reports of the Trypanosomiasis Expedition to the Congo, 1903–1904*, by Dutton, Todd, and Christy)

hard and shotty. Intermediate stages between these extremes occur, and sometimes even in the same area glands in all stages can be felt. All groups of glands are involved, but those in the neck are most conveniently examined. The condition of the scalp of the native is, however, a common cause of enlargement of the cervical lymphatic glands, but large, elastic, painless, and freely movable glands of the kind mentioned above are very characteristic and merit careful examination for trypanosomes. Other groups of enlarged glands, which can easily be recognized clinically, are in the axillae, in the inguinal and femoral regions, in the popliteal space, and in the epitrochlear region. There is no doubt that

- Enlargement of liver and spleen* the infection causes enlargement of the liver and spleen but, as sleeping sickness patients have so often suffered from malaria and other tropical complaints, little importance can be attached to this as a clinical sign of trypanosomiasis.
- Tachycardia* Tachycardia is very constant in an early trypanosomal infection. Even in the apyrexial periods the pulse-rate is usually over 100 per minute.
- Blood-pressure* The arterial blood-pressure is usually low. It is possible that these circulatory phenomena are due to myocardial changes which Peruzzi has shown to be so common in monkeys experimentally infected.
- Skin rash* Erythematous eruptions may appear at any stage of the disease but are particularly common during its earlier stages. They are usually most prominent on the trunk but may extend on to the face and limbs and are much more easily seen on the light skin of the European than on the black skin of the African. Sometimes they assume the form of large irregular patches but often are circinate. Usually they are transient but they may persist for prolonged periods. When the rash fades it leaves no trace and its disappearance is not accompanied by desquamation.
- Oedema* Localized transient oedemas, particularly in the lower eyelids and ankles, may be seen as early as the first few weeks of the disease.
- Albuminuria* Albuminuria is not constant but is found in many cases, not only at the beginning of the infection but throughout its whole course. Some patients exhibit quite early signs of gastro-intestinal disturbances with vomiting and diarrhoea of varying intensity.
- Gastro-intestinal disturbance* As the disease progresses the patient becomes more and more emaciated and asthenic, the slightest effort fatigues him, and he becomes apathetic. He is drowsy during the day-time and frequently falls asleep, but insomnia at night is the rule. Neuralgic pains, muscular cramps, and rheumatic pains in the joints are common. Many patients complain of a sense of tingling in the face, the palms of the hands, the fingers, and the soles of the feet. Hyperaesthesia is often noticed quite early. Deep pressure, such as that which occurs in the palm of the hand when turning a large key in a stiff lock, is followed after a short interval by a degree of discomfort amounting to actual pain (Kérandel's sign). Paresis of one or more muscular groups, particularly of the facial muscles, is not uncommon in the early stages. Coincidentally with these symptoms
- Progress of disease* psychological disturbances develop. The patient becomes irritable, melancholic, emotional, or depressed. Memory fails, there is intellectual degeneration, and the character changes.
- Pain* As the meningo-encephalitic changes progress the patients may exhibit multitudinous nervous signs, such as paresis or paralysis of various muscles or groups of muscles, hemiplegia or paraplegia with incontinence, incoordination of movement, alterations in muscle sense, rigidities, various contractures, epileptiform convulsions, delirium, severe headache, pronounced somnolence, and profound psychological disturbances. Finally, they sink into a state of coma, and death results. Although no part of the central nervous system escapes, different portions of it
- Hyperaesthesia*
- Kérandel's sign*
- Paresis*
- Psychical disturbances*
- Nervous signs in later stages*

seem to be predominantly involved in different cases, with the result that clinically a whole series of nervous types of the disease have been described, such as medullary, cerebellar, cerebral, and psychical.

With the development of nervous manifestations the earlier symptoms tend to become modified. The fever does not entirely disappear but becomes much less pronounced, and there may be long apyrexial periods interrupted now and again by rises of temperature which begin and end suddenly. The tachycardia so characteristic of the early stages

*Changes in
other systems
in later stages*

often becomes less pronounced, but the cardiac manifestations, e.g. bruits, arrhythmia, hypertrophy, or dilatation, develop and are possibly related to the myocarditis to which reference was made on page 276. The erythemas may sometimes persist until the later stages of the disease. Attacks of diarrhoea or dysentery often continue, but the appetite remains unchanged until the final coma. Albuminuria associated with chronic nephritis may persist. The liver and spleen may remain enlarged until death or may return to their normal size. The lymphatic glands tend to become atrophied and sclerosed but some of typical character may be found. The general condition rapidly deteriorates and the emaciation progresses until the patient is reduced to skin and bone.



FIG. 21.—Late case of sleeping sickness with extreme emaciation and somnolence

Although impotence develops early in men, menstruation, as a rule, persists unchanged for a long time in women. Aubert and others, however, have drawn attention to the frequency with which women suffering from sleeping sickness abort or give birth prematurely to dead children.

*Changes in
sexual and
reproductive
functions*

Ocular troubles are not uncommon in trypanosomiasis; one or both eyes may be involved. Cyclitis, interstitial keratitis, and iritis, which are fairly common in the earlier stages of the disease, are due to the localization of trypanosomes in the interstitial spaces of the parts involved; the conditions are as a rule benign and disappear rapidly.

*Visual
disturbances*

There may also be lesions in the depth of the eye involving the retina

*Changes in
retina and
optic nerve*

and the optic nerve. Two kinds of lesion may be exhibited by the optic nerve: the disk may be oedematous as the result of meningeal invasion by the trypanosome or of hypertension of the cerebrospinal fluid; or there may be signs of optic atrophy with pallor and narrowing of the vessels of the disk. These changes may occur in the absence of any arsenical treatment, but optic atrophy with defective vision or even complete blindness is the chief danger resulting from the treatment of sleeping sickness by the aromatic compounds of arsenic.

6.—PROGNOSIS

This varies according to the stage of the disease at which treatment is begun. If the diagnosis is made early the outlook with proper treatment is remarkably good in both *gambiense* and *rhodesiense* infections. Even well advanced cases of *gambiense* infection showing pronounced changes in the cerebrospinal fluid are often cured by adequate treatment. In advanced cases of *rhodesiense* infections the prognosis is not nearly so hopeful.

*Gambiense
infections*

It has long been known that *gambiense* infections may display very varying degrees of virulence. Occasionally patients harbour the trypanosomes for prolonged periods without exhibiting any signs of the disease; in other cases, however, the disease sets in suddenly with violent symptoms and runs a rapidly fatal course.

*Rhodesiense
infections*

As a general rule, the disease produced by *T. rhodesiense* is more violent and runs a more rapidly fatal course in untreated patients than does that produced by *T. gambiense*. It was formerly thought that these differences were sufficient to distinguish the two infections clinically, but it is now recognized that *T. rhodesiense* may produce a very chronic and insidious disease and that *T. gambiense* may produce a virulent and rapidly fatal disease.

7.—DIAGNOSIS

*Isolation of
trypanosomes*

The diagnosis of trypanosomiasis depends, in the early stages at least, upon the discovery of the trypanosomes, and for this purpose the following procedures should be adopted.

*Trypanosomal
chancres*

(i) If the patient presents a lesion resembling a trypanosomal chancre, it should be punctured with a hypodermic syringe and the drop of fluid obtained examined microscopically, either in a cover-slip preparation or as a stained smear. As trypanosomes are readily found in considerable numbers this is a valuable method of making a very early diagnosis. (ii) Blood examination can be carried out on fresh cover-slip preparations or on stained thin or thick films. (iii) If the patient exhibits typical enlarged semi-fluctuating glands, one of the easiest methods of discovering the trypanosomes is by their puncture. The minute drop of fluid removed by means of a hypodermic syringe is examined either as a fresh cover-slip preparation or as a stained thick or thin film.

*Blood
examination
Gland
puncture*

As the result of careful analysis of the figures obtained from the various methods of blood and gland juice examination among 6,273 patients with puncturable lymphatic glands, Raoult concluded that examination of thick blood films gives the highest proportion of positive results and examination of stained gland-juice films the next highest. If both these methods give negative results recourse should be had to the following method of triple centrifugation of large volumes of blood.

(iv) About 5 c.c. of blood are withdrawn from a vein into 1 c.c. of a 1 per cent solution of sodium citrate and centrifugalized at low speed until most of the erythrocytes are thrown down. The supernatant fluid is removed and again centrifugalized at low speed until the remaining erythrocytes and most of the leucocytes are deposited. The supernatant fluid is again removed and centrifugalized at high speed, the deposit being examined microscopically for trypanosomes, in fresh preparations or in stained films. *Triple centrifugation of blood*

(v) In old-standing cases of sleeping sickness, in which trypanosomes are often difficult to discover in the blood and the lymphatic glands are sclerosed and atrophied, lumbar puncture is an invaluable aid to diagnosis. Although trypanosomes are by no means always found in the centrifugalized deposit of such cases, the typical morbid changes shown by the fluid are sufficient to warrant a diagnosis in a suspected case coming from an endemic region. *Lumbar puncture*

8.—TREATMENT

(1)—Prophylaxis

This resolves itself into an attempt to protect human beings from being bitten by infective tsetse flies. Owing to the wide-spread distribution of these flies and to the fact that they bite by day, the problem is one of extreme difficulty. The only satisfactory manner of exterminating the tsetse in an area is by clearing the bush and undergrowth which harbour the fly. In *G. palpalis* country, where the fly is confined to the banks of streams and the shores of lakes, local clearings are made around the villages and at the sites of watering-places and fords. In *morsitans* country, where the fly is widely distributed independently of water, the problem is even greater; clearings are made around villages and on each side of the roads. During the last ten years more ambitious attempts have been made, particularly in Tanganyika, to exterminate tsetse from relatively large areas of country by systematic clearing combined with organized burning of grass. Probably the most hopeful line lies in the concentration of the population from scattered villages into relatively large communities, coupled with extensive clearings around these settlements and along the main routes.

Another method by which the problem has been attacked is the destruction, so far as possible, of the reservoir of the virus from which the fly becomes infected. This method, which has been extensively used in the French and Belgian equatorial colonies, consisted briefly in the *Destruction of reservoir of virus*

treatment of the sick by itinerant missions. The underlying idea was not so much the cure of the patients as the temporary sterilization of their peripheral blood, thereby rendering them non-infective for the tsetse fly. Enormous numbers of infected cases have received these so-called prophylactic injections of atoxyl (sodium aminarsonate). Such a procedure, involving as it did the inadequate treatment of almost countless individuals with an arsenical, is now generally recognized to be undesirable as, apart altogether from its very doubtful value as a prophylactic, it is difficult to conceive of a scheme more calculated to produce arsenic-resistant strains of trypanosomes (see p. 284). Extensive treatment of the infected is undoubtedly a most important prophylactic measure, but treatment is now directed towards the cure of patients instead of the production of merely temporary peripheral sterilization.

Wild fauna

The significance of the wild fauna of tropical Africa as an important food supply of tsetse and as a reservoir of the pathogenic trypanosomes of man and stock is still so controversial as to be beyond the scope of this article.

Drug prophylaxis

The only drug known to have any real prophylactic action is germanin which, in contrast to the aromatic arsenicals, is eliminated very slowly and circulates in the blood for prolonged periods. Duke performed a series of experiments on volunteers and reached the general conclusion that a dose of 2 grams of germanin given to an adult may be expected to confer protection against either *T. gambiense* or *T. rhodesiense* for at least three months.

In 1937 Orlovitch described the result of a large-scale experiment to ascertain the prophylactic action of germanin. The experiment was performed in a district in the Belgian Congo where sleeping sickness was common and where new cases were constantly occurring. In January 1936 every individual in this district was given a dose of germanin (1 gram for an adult). Three months later the population was examined, with entirely negative results. The prophylactic dose of germanin was again administered, and after another three months the population was again examined with negative results, and a third dose of germanin given. The last examination, made three months after the third dose of the drug, failed to reveal a single case of infection.

(2)—Curative

(a) Chemotherapy

Historical

The history of the treatment of sleeping sickness constitutes one of the most remarkable chapters of modern medicine. What was, before 1905, an almost invariably fatal disease can now, if recognized early, be cured with such a degree of certainty that various medical men have deliberately infected themselves and other volunteers with a view to clearing up obscure points in the epidemiology of the disease.

Sodium arsenate

Up to the beginning of the present century the only drug known to have any beneficial action in trypanosomiasis of man and stock was sodium arsenate. The benefits derived from injection of this substance

were, however, transient; relapses followed quickly, and it was found impossible to increase the dose sufficiently to exert a definite effect on the infection without poisoning the host. The first great advance in the therapy of trypanosomiasis was the discovery in 1905 by Thomas, *Atoxyl* at the Liverpool School of Tropical Medicine, that it was possible to effect permanent cures of experimentally infected laboratory animals with atoxyl (sodium *p*-amino-phenylarsonate). This drug was immediately tried with striking success on cases of human sleeping sickness, and for nearly twenty years it remained the chief weapon for treatment. This empirical discovery gave a great impetus to chemotherapy, and during the last thirty years a very large number of trypanocidal substances have been produced. Almost all of these have been organic compounds of arsenic or antimony, but one of them, Bayer '205' or germanin, is a complex urea-substitution compound and contains no heavy metal. Of this long series of compounds four have stood the test of time, and it is on them that reliance is placed at present for the treatment of the disease. These are the aromatic pentavalent arsenical compounds, atoxyl, orsanine, and tryparsamide; and the urea-substitution compound germanin. *Germanin*

Sodium aminarsonate (atoxyl, soamin, trypoxy) is the monosodium salt of *p*-amino-phenylarsonic acid. This drug, which is now almost entirely superseded by the more active and less toxic orsanine, is given, in 10 per cent solution in sterile distilled water, either subcutaneously, intramuscularly, or intravenously. The dose is 10 to 15 mgm. per kilogram of body weight (0.5 to 0.75 gram for an adult), and the injections are given once weekly for about six to twelve weeks. Although this method of treatment cured large numbers of early cases there were many relapses. Increasing the dose to 15 to 20 mgm. per kilogram of body weight gave a larger proportion of cures, but also a large proportion of serious disturbances of vision. Atoxyl proved to be of little use in cases in which examination of the cerebrospinal fluid revealed morbid changes. *Atoxyl*

Orsanine (Fourneau '270') is the monosodium salt of 4-acetyl-amino-2-hydroxyphenylarsonic acid. It is given, in 20 per cent solution in sterile distilled water, either subcutaneously, intramuscularly, or intravenously. The dose is 20 to 35 mgm. per kilogram of body weight (up to 2 grams for an adult), and the injections are given at weekly intervals for ten or twelve weeks. As already mentioned, orsanine has now largely replaced atoxyl because it produces more rapid peripheral sterilization, is followed by fewer relapses, and is less toxic. In the meningo-encephalitic stage of the disease it is of very limited value. *Orsanine*

Tryparsamide (tryponarsyl) is the monosodium salt of N-phenyl-glycineamide-*p*-arsonic acid. It is very soluble and is given in 20 to 40 per cent solution; it is administered intravenously, and solutions should be made in sterile distilled water immediately before use. It is usually given in doses of 20 to 40 mgm. per kilogram of body weight (1.5 to 3 grams for an adult); the doses are given at weekly intervals until a *Tryparsamide*

total of about 30 grams has been administered, after which the drug should be stopped for a period of a month or so. Chesterman used weekly doses as large as 4 grams in adults with changed cerebrospinal fluid, but such doses must be given with great caution owing to the danger of visual disturbance. The general consensus of opinion is in favour of smaller doses, especially at the beginning of treatment of very advanced cases. Although tryparsamide is less active as a trypanocidal substance than orsanine, it has the great advantage of acting in the later stages of the disease when the meninges are involved.

If lumbar puncture shows that the cerebrospinal fluid has not become normal the course of treatment must be repeated. The condition of the cerebrospinal fluid is the essential guide to treatment in the later stages of sleeping sickness, and it is not justifiable to conclude that a cure has been obtained until the cerebrospinal fluid has returned to normal and has remained so for at least six months.

Germanin

Germanin (Bayer '205', moranyl, and antrypol) is a complex urea-substitution compound not containing any heavy metal. Germanin is a slowly acting, but exceedingly valuable, trypanocidal substance. The compound is usually given intravenously in 10 per cent solution in sterile distilled water. The customary dose is about 1 gram for an adult, but doses as large as 1.5 grams or even 2.0 grams have been employed. The doses are usually repeated at intervals of two or three days until a total of 10 grams has been administered.

*Response of
gambiense
and
rhodesiense
infections*

Gambiense and *rhodesiense* infections differ in their response to drugs. Generally speaking, *gambiense* infections are sensitive to the aromatic arsenicals and to germanin whereas *rhodesiense* infections, although sensitive to germanin, are relatively resistant to the aromatic arsenicals.

*Importance
of early
treatment*

Another point to be borne in mind is that the disease is much more easily cured in its early stages than later on when there are pronounced nervous lesions. In fact, before the advent of tryparsamide, the great majority of advanced cases ran their course to the inevitable termination; in all cases exhibiting morbid changes in the cerebrospinal fluid tryparsamide should be used.

*Rules for
treatment*

Bearing these facts in mind it is possible to lay down the following rules for treatment.

Gambiense

Gambiense infections: early cases with normal cerebrospinal fluid should be treated with orsanine or germanin; later cases with pathological cerebrospinal fluid should, after a few preliminary doses with orsanine or germanin to produce peripheral sterilization, be treated with tryparsamide.

Rhodesiense

Rhodesiense infections: early cases should be treated with germanin. Owing to the relative resistance of these infections to arsenicals the treatment of later cases of *rhodesiense* infections, with pathological cerebrospinal fluid, is much less satisfactory than is the treatment of corresponding cases of *gambiense* infections. The best results are obtained from a combined treatment with germanin and tryparsamide.

(b) Toxic Effects of Arsenic and Germanin

Both the pentavalent aromatic arsenicals (atoxyl, orsanine, and tryparsamide) and germanin may produce toxic signs and consequently must be used with care. Occasionally the aromatic arsenicals produce gastro-intestinal symptoms with vomiting and acute diarrhoea, but these are generally transient and cease when the drug is stopped. Other rare toxic effects are disturbances of hepatic function and dermatitis. The most serious accident resulting from the arsenicals is damage to the optic nerve. Disturbance of vision may develop gradually or suddenly, and it is always necessary to inquire carefully regarding the sight of the patient when administering a course of treatment with one of the arsenical compounds. The first signs of damage to the optic nerve are dimness in acuity and narrowing of the fields of vision; the patient may also complain of mists and sometimes of flickerings. Scotoma, either central or peripheral, indicates a more advanced stage of damage. As a rule, if the condition is recognized early and the drug immediately stopped, the sight is restored, but the damage is sometimes progressive and continues until the sight is completely lost. In the early stages the ophthalmoscope may fail to reveal any change, and it is only after the sight is permanently damaged, or completely destroyed, that the appearances of optic atrophy are seen. The precise cause of this catastrophe is still obscure, but there seems no doubt that there are two factors at work, namely, the meningeal lesions produced by the disease, and the drug. Patients with considerable meningeal involvement are more likely to develop disturbance of vision when treated by an arsenical than are early cases, and consequently the greatest care is necessary when treating advanced cases of the disease.

There is some evidence that visual disturbances following the administration of an aromatic arsenical may be benefited by a course of sodium thiosulphate: 10 c.c. of a 20 per cent solution given intravenously on alternate days. Remarkable success is claimed by Raingeard who treated in this way a series of twenty-six patients with recent or old-standing ocular troubles, twelve being blind, after the administration of atoxyl or tryparsamide.

The most common and serious toxic effect of germanin is damage to the renal epithelium. A considerable proportion of patients treated with this drug develop albuminuria after the administration of a number of doses. As a rule it is transient and is not accompanied by any concomitant symptoms; sometimes, however, the condition is more severe and on centrifugalizing the urine there may be a deposit containing red cells and granular casts. Cessation of treatment generally causes these signs to disappear or diminish, but they may reappear when the treatment is renewed. Occasionally, very severe renal damage occurs with uraemia, anuria, and death. A very much rarer toxic effect of germanin is dermatitis.

(c) *Drug-Resistance*

If a laboratory animal infected with trypanosomes is given a sub-curative dose of atoxyl the trypanosomes disappear from its blood for a time, but a relapse occurs; if another similar dose of the drug is then given the trypanosomes again disappear, but return after a shorter interval. If the process is continued a state is eventually reached when even the largest dose of the drug which the host will tolerate fails to exert any influence on the infection, because the trypanosomes have become atoxyl-resistant.

The phenomenon of drug-resistance has been the subject of much work since 1929 (Yorke *et al.*, 1929-38). It is now known that a strain of trypanosomes which has become resistant to any one of the aromatic compounds of arsenic is also resistant to all the other commonly employed aromatic compounds of arsenic or antimony, but not to germanin. Resistance to the aromatic compounds of arsenic is readily acquired, whereas resistance to germanin develops very slowly. When once a strain of trypanosomes has been made resistant to atoxyl, orsanine, or tryparsamide, it retains its resistance indefinitely, and there is no known way of destroying the resistance; the resistance is not lost by changing the species of host, or after repeated cyclical transmission through *Glossina*.

To what extent arsenic-resistance results from treatment of human trypanosomiasis is at present unknown, but there seems no reason to doubt that inadequate treatment of infected human beings by one of the aromatic arsenicals may well result in the production of an arsenic-resistant strain of trypanosomes. As resistant strains pass unchanged through their cyclical evolutions in the tsetse, the possibility of the dissemination in man of infections which cannot be cured by arsenicals must be borne in mind. Recently a considerable number of strains of *T. gambiense* obtained from man from different endemic areas in Africa have been examined, and certain of them have been found to exhibit considerable degrees of resistance to tryparsamide.

It must not, however, be assumed that every case which fails to be cured by an adequate course of an arsenical is infected with a resistant strain of parasites. The explanation of the failure to cure certain of these cases appears to be the extensive and deep-seated nature of the infection. Much further work is required on this very important subject.

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TSETSE FLY DISEASE

See TRYPANOSOMIASIS, p. 263

TSUTSUGAMUSHI DISEASE

See TYPHUS FEVERS, p. 347

TUBERCULOSIS

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Reference may also be made to articles on individual organs (e.g. the kidneys) and to the following titles:

LUNG DISEASES:

TUBERCULOSIS

LUPUS VULGARIS

MENINGITIS

SILICOSIS

SKIN DISEASES:

TUBERCULOSIS

TROPICAL DISEASES, .

GENERAL SURVEY

TUBERCULOSIS,

GENERALIZED

1.—AETIOLOGY AND BACTERIOLOGY

(1)—The Tubercle Bacillus

1554.] This bacterium belongs to the acid-fast group, *Mycobacterium*, which retain carbol fuchsin stain after treatment with acids (Ziehl-Neelsen method). It grows slowly at body temperature on complex

media, usually containing egg yolk, but it does not multiply at room temperature though it can survive in dried sputum and on soil and grass for months. It is destroyed by pasteurization (low temperature holding process at 65° C. for thirty minutes).

Three strains infect man, namely, avian, bovine, and human. The avian strain is found in the domestic fowl and readily infects pigs but is very rare in man. The bovine strain occurs chiefly in dairy cattle, is not uncommon in pigs, is rare in sheep and goats, and readily infects man. The human strain occurs only in man. In countries where raw milk is not drunk bovine infection is rare and in tropical countries it is very rare. Native cattle are not immune but are seldom affected unless European stock is introduced.

Statistics collected from the world's literature by Gervois show that the bovine strain has been found in man in the following percentages of the total tuberculosis investigated in different countries: Hungary 1·7, Canada 2·0, Japan 2·9, Argentina 3·2, Italy 3·5, Poland 5·6, Norway 6·5, France 6·8, Switzerland 7·7, Holland 8·9, England 10·4, Germany 10·8, United States 11·7, Australia 12·1, Denmark 13·9, and Scotland 20·7. The English figures, analysed by Griffith, show that the bovine strain was found in 50 per cent of cervical gland tuberculosis, 48·7 per cent of lupus, 24·6 per cent of meningeal cases, and 19·5 per cent of bone and joint cases. In Scotland these figures are all slightly higher. In pulmonary tuberculosis, bovine strains have been found in England to be from 0·52 to 1·6 per cent and in Scotland 4·6 to 8·5 per cent. The percentage of milk samples containing tubercle bacilli varies in different countries. In England it is 7·9, in Europe generally 8·7, and in the United States 8·5 (Gervois). For abattoir statistics the reader is referred to Savage.

By frequent subculture strains of permanently low virulence have been obtained. The best known is the bovine strain *Bacille Calmette-Guérin* (B.C.G.) used as a prophylactic vaccine of living organisms (see p. 295).

A filter-passing virus produced by the tubercle bacillus has been described, but the proof of its existence rests on dubious evidence.

(2)—Channels of Infection

Of the four possible channels, namely, respiratory tract (including conjunctiva and accessory sinuses), digestive tract, skin, and genito-urinary tract, the first two only are important. Genito-urinary tuberculosis is practically always blood-borne, and cutaneous infection, e.g. anatomist's wart, is rare; the portal of entry in lupus is still obscure.

Bacilli reach the respiratory tract by inhalation of dried infected dust and droplets of saliva and sputum expelled by coughing. They enter the digestive tract by uncooked infected food, chiefly raw milk, and the use of infected articles such as crockery and table utensils. Fewer bacilli are required to infect the respiratory than the digestive tract.

The primary focus is most commonly in the respiratory tract and

*Primary focus**Endogenous and exogenous reinfection*

usually occurs in childhood, but those who escape infection in childhood may develop a primary infection later, usually in early adult life (Wallgren). Adults who were infected in childhood and were thought to have recovered may break down again from a partially healed smouldering focus (endogenous reinfection) or from a superinfection from without owing to low resistance (exogenous reinfection); but these terms are not very satisfactory because usually it is impossible to determine clinically precisely what has happened.

2.—EPIDEMIOLOGY

Incidence of infection

The large majority of the inhabitants of civilized countries have been infected with the tubercle bacillus by the time they reach adult years. A recent survey of a large group of London children (Dow and Lloyd) showed that the Mantoux test is positive at 0 to 5 years in 23 per cent, at 5 to 10 years in 39 per cent, and at 10 to 15 years in 58·3 per cent.

Influence of exposure

The degree of exposure affects the incidence of infection and it was found that in the group 0 to 5 years contacts of open cases of pulmonary tuberculosis were infected five times as often as those not so exposed.

Influence of locality

The incidence of infection in adults varies greatly in different parts of the world; in isolated rural districts less than half the population may be infected whereas in large towns the prevalence of infection was, until recently, almost universal. The rapid decline in the number of open cases of tuberculosis and the decrease in the amount of unpasteurized milk now consumed have reduced the sources of infection, with the result that even in large cities an increasing proportion of young adults are free from any evidence of infection. Although an essential preliminary, the incidence of tuberculous *infection* has very little connexion with that of tuberculous *disease*.

Influence of milk

Age has great influence not only on the mortality but on the type of disease most prevalent. Very high death-rates were formerly met with in young children but these have fallen considerably. In New York City the mortality rate from tuberculosis for infants under one year fell from more than 500 per 100,000 in 1900 to 50 in 1932 (Drolet). The lowest death-rates of all are found in children from 10 to 15 years of age although this is an age at which there is a rapidly increasing amount of tuberculous infection.

Age

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Relative incidence in age groups

In children, deaths from non-pulmonary forms of tuberculosis greatly outnumber those from pulmonary tuberculosis, meningitis being particularly common in young children within a few months of exposure to massive infection. Pulmonary tuberculosis continues to be the most important cause of death between the ages of twenty and forty; three main types of the disease have been recognized: (i) the young adult type, which is less common where there is much childhood tuberculosis and infected milk; this is a relatively acute form prevalent mainly in women and especially in rural districts; (ii) a middle-age type, which

is closely correlated with the general death-rate and therefore dependent on hygiene (Brownlee); and (iii) an old-age type.

Social conditions play a very important part in the incidence of pulmonary tuberculosis, the disease being much commoner in overcrowded areas. Nutrition is even more important, as has been shown by the fact that the disease has been seen to increase when a slum clearance scheme resulted in higher rents and therefore less money for food. Much may also be learned from the study of mortality according to occupation, that of unskilled labourers being eight times as high as in professions giving a higher standard of life, e.g. clergy, doctors, and lawyers. The Great War also illustrated the influence of privation on tuberculosis; most countries showed a check in the previously rapid fall in the mortality rate, and those in which food shortage was severe, notably Germany, Austria, and Hungary, showed a considerable increase in the number of deaths from tuberculosis both during and shortly after the War. *Social conditions*

In a non-industrial nation in which pulmonary tuberculosis has been long established and endemic, the maximal incidence is late in life. As such a nation becomes industrialized this maximal incidence moves to early adult life. Males are more affected than females. When the community settles down to the new conditions, the incidence recedes again to the later years. Industrial areas may then, owing to better organized social hygiene, enjoy a lower death-rate than rural. In England, three groups of industries show a high tuberculosis death-rate (Collis): (i) boot operatives, printers (Hill), and tailors, probably as the result of recruiting from less robust types; (ii) commercial travellers, and innkeepers and their servants, as the result of chronic alcoholism; and (iii) workers exposed to dusts containing free silica, SiO_2 , or certain silicates such as asbestos (see Vol. II, p. 138). The incidence in coal miners is only high when there is exposure to silica (see also SILICOSIS, Vol. XI, p. 138). *Industrial tuberculosis*

The well known fact that often several members of one family die from pulmonary tuberculosis has led to the belief that it is a hereditary disease, the tuberculous diathesis being often mentioned in the literature of a generation or two ago. Although the present tendency is to regard infection from open cases in the family as more important than hereditary disposition, some support to the diathesis hypothesis has been given by the work of Kretschmer who found that short thickset individuals, his pyknic type, were less likely to contract tuberculosis and more likely to recover from it than his other two types, the athletic and asthenic. (See also HEREDITY AND CONSTITUTION, Vol. VI, p. 467.) *Heredity*

Kretschmer's physical types were found to show well marked differences in character, a thickset body tending to go with an extrovert type of mind. The athletics and asthenics were more likely to suffer from schizophrenia and it has been observed independently that sufferers from this form of psychosis often die of tuberculosis. The *Mental factors*

large number of men and women of genius who have died from tuberculosis has given rise to the opinion that the toxins of the disease may stimulate creative effort. It seems more likely that the mind of the genius exhausts his body and reduces its resistance to tuberculosis as, in the majority of cases, there was evidence of genius before symptoms of tuberculosis became apparent.

Climate

Climatic influences are difficult to disentangle from those of race and hygiene, but there is reason to believe that tuberculosis occurs more readily in moist warm climates than in cold dry ones. This is clearly shown in India where desert regions show a low mortality from pulmonary tuberculosis and a high one for pneumonia, the reverse being the case in the humid coastal area near Madras (Rogers). Tuberculosis is also rarer in high Alpine villages than in low-lying valleys, and in England more common where there is exposure to the rain-bearing south-west wind than in places with better shelter or a different aspect. Damp impervious soil may also play a part, but the evidence for this is inconclusive.

Contact

Since the discovery of the tubercle bacillus, the importance of contact infection, particularly in childhood, has largely displaced the former hypothesis of hereditary diathesis. In more than 80 per cent of infants dying from tuberculous meningitis the source of infection can be traced to an open case of pulmonary tuberculosis in the family, and in many families in which there are several cases of pulmonary tuberculosis in brothers and sisters there is evidence of massive childhood infection (Opie and McPhedran). The study of latent apical tuberculosis has shown that radiological signs of tuberculosis are much commoner in those exposed to infection than in the general population and that an appreciable proportion of those cases proceed to the stage of active pulmonary tuberculosis (Opie and McPhedran). Prolonged exposure to infection is usually required, the average period before tuberculous glands at the roots of the lungs become evident being four and a half years, and the average time preceding latent apical tuberculosis nearly nine years. Although children, and particularly infants, are in great danger of acquiring an acute form of the disease, morbidity by no means always follows infection and approximately one-sixth only of the children becoming tuberculin-positive during the first year of life die from the disease. Although the incidence of pulmonary tuberculosis is much higher in some families than in others it has been found that in tuberculous families, particularly when the mother is affected, the prognosis of the survivors is better than when there is no family history (Ford).

Conjugal infection

There is considerable difference of opinion as to the risks run by the unaffected husband or wife of an open case. Fishberg, in a large series of cases, found no evidence of any increase in morbidity above the average. Most other authorities find a definite increase and Opie and McPhedran in their study of latent apical tuberculosis found as high a proportion as ten out of twenty-one showing evidence of pulmonary

infiltration. Although there can be little doubt that conjugal infection does occur it does not appear to be very common.

An investigation of the problem of the contagion of pulmonary tuberculosis to doctors, nurses, and domestic staff at the Brompton Hospital for Consumption and Diseases of the Chest between the years 1846 and 1882 showed no evidence of increased morbidity (Williams); this is all the more surprising in view of the fact that neither ventilation nor disinfection of sputum had any part in the treatment of the disease at that time. Even at the present day the medical profession has a particularly low mortality from tuberculosis, but there is increasing evidence that infection of nurses and medical students occurs. Much light has been thrown on this apparent discrepancy by Heimbeck of Oslo, who found that out of 625 nurses Pirquet-positive on arrival there was no death from tuberculosis and only 27 presented any signs of morbidity. In contrast to this group, in 280 nurses Pirquet-negative on arrival there were 10 deaths from tuberculosis and 96 showed signs of activity. The comparative morbidity rates have been worked out as follows:

Pirquet + on arrival at hospital	8.5	per 1,000 observation years			
Pirquet -	152.9				

*Doctors,
students,
and nurses*

From these figures it may be concluded that, whereas there is grave danger of previously uninfected nurses contracting tuberculosis in hospital, the evidence provided by this investigation does not suggest that nurses who have already overcome the usual childhood infection are any more likely to contract the disease than members of the general population.

The study of the mortality rates for all forms of tuberculosis in England and Wales shows an almost continuous decline from over 350 per 100,000 in 1861, when accurate records began, to 69 per 100,000 in 1936. It is probable that this mortality rate reached its peak somewhere about the middle of the 19th century. Annual returns show that in Ireland the mortality rate, after being considerably lower than the rest of the British Isles during the greater part of the 19th century, reached its peak in 1900 since when it has been falling rapidly. In certain countries, e.g. Porto Rico, the wave of tuberculosis is still rising. In Sweden, Neander has shown that in the early years of the 19th century deaths from tuberculosis were most common in the districts near Stockholm and least in Norbotten in the rural north. A century later the position was reversed, Norbotten having far the highest rates in the whole country. The most probable explanation of the change which has taken place in this province is that until the recent improvement in communication there was so little intercourse between the scattered villages and farms that there was very little contact with the tubercle bacillus. It is significant that bovine tuberculosis was also practically unknown in Norbotten even at a time when pulmonary tuberculosis was causing a high mortality.

*The epidemic
wave*

3.—IMMUNITY AND ALLERGY

*Immuno-
logical groups*

Cummins classified mankind into three immunological groups: (i) primitive tribes with no experience of the disease exhibiting an unmodified or 'natural' tuberculosis (e.g. Senegalese troops in the World War); (ii) European races well salted by centuries of exposure showing 'modified' types of disease; and (iii) stocks with an intermediate immunological experience having a 'larval' form (e.g. native workers in South African mines). The disease is acute and rapidly fatal in the first group, chronic and liable to heal in the second, and less chronic and generally progressive in the third.

*Factors
governing
resistance*

Resistance also varies in members of the same racial stock; this immunity is individual, acquired, and non-transmissible. Examples of a favourable soil for the bacillus are seen in altered metabolism, e.g. diabetes mellitus, and of an unfavourable in hyperaemia and congestion, e.g. valvular disease of the heart. The chief factors in resistance are anatomical protection of a portal of entry, e.g. turbinates; cellular, e.g. phagocytosis; and humoral, e.g. various antibodies. Possibly endocrine secretions and enzymes also assist. Little is known of the size of the infecting dose of bacilli; it is assumed that small doses tend to protect, large doses to produce disease. Considering the problem as a whole the invasion of a community by tuberculosis appears to be followed by a very high death-rate, particularly among young adults, and acute and generalized forms are frequent. Adults who have overcome a primary childhood infection will still be susceptible. The development of resistance takes several generations, during which almost the whole population is infected with the tubercle bacillus, the more acute type in young adults giving place in frequency to the pulmonary tuberculosis of middle age. With the fall in the number of open cases infection of the population becomes less universal, and those not infected in childhood run an increased chance of contracting pulmonary tuberculosis if exposed to massive doses in early adult life.

Allergy

Allergy is a state of partial immunity, a changed reactivity to the tubercle bacillus and its toxins as a result of previous infection with the organism. This changed reactivity is generally a hypersensitivity.

*Hyper-
sensitivity*

In the experimental animal a difference can be recognized between the effects of primary and of subsequent infections. Cummins (1934) recognized three stages: (i) indifference, immediately following infection; (ii) intolerance, brought about by escape of toxins from a primary focus into surrounding tissue; and (iii) tolerance, in the late stages. Rich considered that allergy was neither synonymous with nor essential to immunity. In the fortuitous infection of man these distinctions are not so clear-cut and allergy is used loosely for any form of toxæmia occurring after the time of primary infection. Desensitization is the diminution of hypersensitivity by clinical means such as the injection

*Desensitiza-
tion*

of protein (e.g. tuberculin shock). It is usually temporary in effect and does not necessarily prevent the disease from progressing.

4.—MORBID ANATOMY

The cardinal signs of the tuberculous lesion are (i) exudation of serous fluid, usually into synovial and serous spaces; (ii) infiltration of tissues with discrete tubercles; (iii) coalescence of these into caseous masses; (iv) liquefaction of caseous areas (cold abscess); (v) fibrosis; and (vi) calcification. *Cardinal signs*

The first lesion produced by the bacillus after passing the portal of entry is referred to as the primary focus (Ghon focus, *primär Komplex*). It is generally found in the lung or a mesenteric gland but may occur anywhere. Usually it is a small nodule about the size of a pea which heals by fibrosis and calcification but may grow and form satellite lesions by lymphatic spread. From any of these lesions further extension may follow: (i) along an open channel, e.g. bronchogenic spread; (ii) by occasional small emboli to distant organs, e.g. kidneys, bones, and joints; or (iii) by generalized haemic infection, e.g. tuberculous bacillæmia. The last two methods are characteristic of the acute lesions of childhood. The lesion of progression is caseation, the lesion of retrogression is fibrosis. The disease may progress in one lesion while retrogressing in another. Secondary infection with pyogenic organisms resulting in true suppuration may supervene at any stage and is frequently followed by amyloid degeneration. The survival time of the bacilli in obsolescent lesions is not known but is probably years. *Ghon focus*
Extension from primary focus

The picture presented at necropsy is composite with almost any combination of the above lesions. Statistics of prevalence of tuberculosis in necropsies at all ages are mostly old and unreliable. At Edinburgh Royal Infirmary (1926–7) Todd found tuberculosis in 69 per cent of the necropsies including 9 per cent with active lesions (excluding deaths from tuberculosis). *Necropsy findings*

The cellular response to the tubercle bacillus is two-fold—phagocytic and connective-tissue producing. The unit of the tuberculous lesion is a nodular collection of macrophages known as epithelioid cells with an outer rim of collagenous fibrils. In this minimal lesion may also be found a giant cell near the centre, a few tubercle bacilli, and a zone of small round cells outside the collagenous fibrils. This unit takes about ten days to develop. It may then gradually heal by the collagenous fibrils replacing the phagocytes until it becomes a fibrotic nodule or it may enlarge until it is visible to the naked eye as a miliary tubercle. In the process of growth, surrounding capillaries are compressed and obliterated, so that penetration by tissue fluids is difficult: this is important in assessing the value of chemotherapy. Caseation, a form of cell necrosis resulting in an accumulation of coagulated proteins and fats, follows. Liquefaction is due to the action of an autolytic ferment *Histology*
The tubercle
Caseation, liquefaction, and calcification

present in the caseation. All caseation, however, does not liquefy. Instead it may be gradually replaced by the deposition of calcium salts and growth of the outer connective-tissue layer. Tuberculous lesions are essentially the same in histological structure wherever they are formed, but modifications may occur as an adaptation to local circumstances, as in the eye and skin.

5.—PROGNOSIS

<i>Leucocyte counts</i>	Leucocyte counts and the sedimentation rate are employed to estimate activity but are valueless for diagnosis. The following are the usual methods: (i) correlation of the ratio of polymorphonuclears to lymphocytes, and lymphocytes to monocytes in the differential white count.
<i>Differential count</i>	In the assessment of these two ratios an increase in the monocytes is regarded as indicating tubercle formation, the polymorphonuclears activity (i.e. caseation and liquefaction), and the lymphocytes quiescence; basophils are neglected and eosinophils added to the lymphocytes as a good prognostic sign; this poly-lymph-mono ratio, or P.L.M. ratio, is expressed as $P + M - 2L$; (ii) estimation of the number of lobes in the nuclei of the polymorphonuclear cells on the assumption that an increase of cells with only one or two lobes, 'left shift', indicates cell destruction and repair and therefore activity; von Bonsdorff's method of estimation, now generally used, consists in the enumeration of the total number of lobes in the nuclei of 100 consecutive polymorphonuclear cells, the normal being regarded as 275 and lower numbers suggesting activity (see also Vol. II, p. 479); (iii) the sedimentation rate, the technique and interpretation of which are described in Vol. II, p. 491.
<i>Arneth index</i>	Houghton has combined the results of the three tests described above in a formula known as the haemogram. The sedimentation rate and P.L.M. ratio are added together as evidence against the patient and this total is deducted from the von Bonsdorff figure as evidence in favour of the patient: $V.B. - [S.R. + (P + M - 2L)] = \text{Index}$. This index varies from a maximum of 300 in the best cases to approximately zero in the worst. Any figure above 260 may be regarded as satisfactory. Patients with an index below 200 are regarded as bad risks from the point of view of operation, e.g. thoracoplasty.
<i>Sedimentation rate</i>	
<i>Haemogram</i>	

6.—DIAGNOSIS

<i>Detection of tubercle bacilli</i>	By means of the Ziehl-Neelsen stain tubercle bacilli may be found in sections of tissue, direct films, or deposits from centrifugalized or sedimented fluids; and in material, such as sputum, faeces, or blood, which has been broken down by digesting fluids so that the bacilli are concentrated into a small bulk. In cases in which sputum is not present
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milk, it should not be difficult to eradicate this disease either by pasteurization or by the use of milk from tuberculin-tested herds. For the grading of milk as specified in the Milk (Special Designations) Order, 1936, see Vol. VII, p. 155. The adult with chronic pulmonary tuberculosis is the main source from which the human bacillus is spread. The use of the sputum flask or of paper handkerchiefs which are promptly burned and the holding of a handkerchief in front of the mouth during coughing or sneezing are the most important hygienic measures directed towards the prevention of spread. In spite of these precautions children are usually infected when there is an open case in the house, especially where cubic capacity and ventilation are inadequate. Sanatorium treatment, in which is included the closure of cavities by collapse therapy in suitable cases, helps considerably in limiting the spread of infection but it is not possible to keep a large proportion of cases in institutions until the sputum is negative. Some local authorities have schemes for boarding out the children when an open case returns home.

Hygiene

*Sanatorium
treatment*

*Maintenance
of general
health*

The maintenance of the general health is of particular importance in family contacts and in those heavily exposed to infection in the course of their work, e.g. sanatorium nurses. The provision by local authorities of extra nourishment to tuberculous patients and their families is an attempt to break the vicious circle by which the presence of pulmonary tuberculosis in the bread-winner so often reduces the money available for food just at a time when the children need to be in a particularly good state of resistance to infection. In spite of these measures poverty and consequent malnutrition remain potent factors in favouring the spread of tuberculosis.

*Early
diagnosis*

*Radiological
signs*

Unsuspected cases are a great source of danger to others and it is regrettable that a considerable proportion of cases when first diagnosed have obviously been suffering from the disease for a long time. D'Arcy Hart has called attention to the fact that radiological signs are present before symptoms have appeared and that it is therefore useless to expect to make an early diagnosis if it is left to the patient to request an examination when he feels ill. Serial X-ray examinations of the whole population are obviously impracticable, at any rate at present, but there is much in favour of periodic radiological examinations of selected groups of individuals more likely than the average to contract tuberculosis. Such groups would include contacts of open cases, young nurses, medical students, and diabetics.

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TUBERCULOSIS, GENERALIZED

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Reference may also be made to the following titles :

LUNG DISEASES: TUBERCULOSIS
TUBERCULOSIS

1.-DEFINITION AND NOMENCLATURE

1555.] The term generalized tuberculosis implies the coexistence of tuberculous lesions widely disseminated throughout many organs in the body. Such a condition is common in some animals as a manifestation of experimental tuberculosis and also occurs in the natural disease in certain species, for instance the pig and horse (Cobbett). In man it is much commoner to find tuberculous lesions in many organs at necropsy than to be able to demonstrate or infer their existence during life. Generalization of the disease in such cases often has no clinical importance. Krause regarded it as not uncommonly benign, though often it is significant of an acute and terminal dissemination of the

organisms. In contrast to these cases, however, there are others in which it is obvious that wide-spread lesions contribute to the manifestations of the disease: to these examples the term generalized tuberculosis applies in a clinical sense. The most important manifestations are seen during childhood when death from tuberculosis is almost always due to generalization of the disease.

There is still great confusion in the literature of generalized tuberculosis upon the question of terminology. The terms 'generalized' or 'disseminated' are in commoner use now than formerly, but forms that properly should be classified in this way are sometimes described as 'haematogenous' or 'miliary', as though all these terms were synonymous. The term 'haematogenous' has the disadvantage that it implies a knowledge of the precise mode of origin of the lesions, a knowledge which often has to be assumed during life and cannot always be established at necropsy. It is incorrect also to regard all examples of generalized disease as haematogenous; some of them owe their origin to spread by lymphatics and may remain throughout confined to the lymphatic system. Similarly, miliary tuberculosis is not synonymous with generalized tuberculosis, for there are massive as well as miliary forms of the latter. Moreover, miliary tuberculosis, particularly the chronic forms, is not always a generalized disease.

Nomenclature

2.—TIME AND METHOD OF GENERALIZATION

Ranke distinguished three successive stages in the course of human tuberculosis. Primary infection initiates a phase in which the disease is confined to lymphatics; subsequent activity is marked by a striking tendency to distribution by the blood-stream; finally, if there is survival, a later phase ensues in which focal extension of one or more of the resulting lesions dominates the course. Generalization of the disease may occur at any time in this cycle but is commonest during the secondary stage. This form is sometimes described as 'early' generalization and includes generalized tuberculosis with a distribution confined exclusively to the lymphatic system and also those forms with a haemic distribution occurring especially in early infancy and childhood. Generalized tuberculosis of the latter type, however, also occurs as an occasional complication of the tertiary stage, through the accidental involvement of the blood-stream by a focal lesion invading an artery or vein—the 'late' form of generalization. Generalized miliary tuberculosis complicating chronic pulmonary tuberculosis is an instance.

Generalization in relation to stages of tuberculosis

The exact character no less than the actual occurrence of a generalized tuberculosis depends upon many factors other than the mode of dissemination of the organisms. Some organs, for example the stomach and pancreas, appear to be relatively immune to the proliferation of the tubercle bacillus and commonly escape any material involvement. The number of organisms disseminated either by lymphatics or by the

Factors promoting generalization

blood-stream has an obvious bearing upon the outcome; if this is not overwhelming in the first instance, the frequency of repetition also becomes an important factor. There is much evidence now to show that recurrent dissemination of organisms occurs by way of the blood-stream, and Schürmann used the term 'protracted progressive dissemination' when describing its effects in the tuberculous.

*dence of
generalization
in children*

In children Blacklock found that generalized miliary tuberculosis is commonest in the first five years of life after a primary thoracic tuberculosis due to human tubercle bacilli. Three examples of primary thoracic lesions due to bovine bacilli were all associated with generalized miliary tuberculosis. After primary abdominal tuberculosis, whether due to infection with human or bovine strains, generalization is commoner in infants up to two years than in older children. Wide-spread dissemination of the disease was found to be commoner after primary abdominal lesions due to human strains than with those due to bovine strains, though the latter led more often to peritonitis and extensive involvement of lymphatic glands. Blacklock showed that generalization is commoner after infection with human than with bovine strains of organism, the human type of infection apparently being more virulent in the child so far as generalization of the disease is concerned. This tendency to generalization is most marked in primary thoracic lesions due to the human type of bacillus and is least marked in primary abdominal lesions due to the bovine type of bacillus.

3.—MILIARY AND MASSIVE TYPES

Two forms of generalized tuberculosis can be distinguished: (i) in which the individual lesions are composed essentially of elementary tubercles scattered widely and often symmetrically throughout many organs—generalized miliary tuberculosis; and (ii) in which the individual lesions are formed by the massive conglomeration and localized extension of a limited number of tubercles occurring in several or even many organs; this may be designated generalized massive tuberculosis. Both miliary and massive types occur as acute and as chronic conditions. Moreover, each form apparently may arise by lymphatic or haemic spread.

*Generalized
massive
tuberculosis*

*Acute
miliary form*

Acute generalized miliary tuberculosis is by far the commonest form of the generalized disease, and occurs most often in young infants or children within a short time of a severe primary infection. At a later age it occasionally complicates any active focal tuberculosis. An older caseous focus is always present and there are many studies, dating from that of Weigert (1882), in which the point of invasion of the blood-stream has been accurately traced from a caseating focus, often in a lymphatic gland or the thoracic duct (Longcope). Generalized tuberculosis with massive lesions is rare except in infants and as an expression of the disease in negroes and other primitive races.

4.—MORBID ANATOMY

Miliary type

Miliary tubercles appear as innumerable grey semi-translucent or yellowish opaque foci scattered uniformly throughout many organs, particularly the lungs, meninges, spleen, kidneys, liver, bone marrow, and the serous membranes. Microscopically they show a typical structure composed of giant cells, epithelioid cells, lymphocytes, and as a rule tubercle bacilli. Inflammatory effusions may occur in any serous sacs involved and are generally not purulent though they contain an excess of leucocytes with a predominance of lymphocytes.

Miliary tubercles

Although miliary tuberculosis is usually rapidly fatal it may run a chronic course, or even heal. Often the miliary lesions are then confined to the lungs, though in some instances other organs are affected. In these chronic cases the miliary foci are firm, fibrous, or even calcified, project from the cut surface of organs, and are opaque and grey or dull white in colour. Sometimes, by fusion, they become individually bigger than usual, the '*grossknotige Miliartuberkulose*' of German writers. Alveolar emphysema around the lesions is common and may become extreme, leading to the formation of numerous small superficial bullae (Pagel).

Chronic and healed lesions

There do not seem to be any recorded examples of acute generalized miliary tuberculosis of entirely lymphatic distribution (though see Braunschweig, 1918). But a very rare form of chronic miliary tuberculosis of this type has been described in detail by Burnand, Schürmann, Pagel, and Hoyle and Vaizey. In this form the miliary lesions are confined to lymphatic channels and lymphatic glands, producing a wide-spread network of fine fibrous tissue in addition to fibrous miliary nodules ('hyperplastic lymphangitis' or 'lymphangitis reticularis chronica'). Within the thorax the lesions involve the lymphatic glands in the mediastinum and extend into the lungs along the lymphatic channels in the sheath of connective tissue common to the bronchi, bronchioles, and their related pulmonary arteries, reaching the finest ramifications in the walls of the alveolar passages and infundibula. This type of miliary granulomatous tuberculosis can only be separated with certainty from the haematogenous type by microscopical examination, which shows its characteristic distribution.

*Miliary lesions restricted to lymphatic tissue**Massive type*

Generalized tuberculosis with massive lesions affects more particularly the lymphatic system, serous sacs, and spleen. In its extreme forms it is a definite morbid entity, consisting of a general adenitis with or without a multiple serositis, and also scattered lesions varying from submiliary tubercles to massive caseous areas in the lungs, spleen, and other viscera. The involvement of serous membranes leads to inflammatory effusions or extensive adhesions in both pleural cavities, pericardium, or peritoneum, sometimes concurrently as one form of polyserositis.

Involvement of serous membranes

The spleen is commonly enlarged and may be huge. As the glandular involvement includes tracheobronchial and abdominal lymphatic glands as well as superficial groups, various secondary effects may occur from mechanical pressure or caseous invasion of adjacent structures. There may thus appear such diverse sequelae as bronchial obstruction with pulmonary collapse, chylothorax, intestinal obstruction, or elephantiasis of the leg. Ulceration of caseous mediastinal glands into a bronchus may produce in turn a caseous tuberculous pneumonia. Among the more chronic examples tuberculous iritis is common. The lesions may remain firm caseous foci which in time become obsolete and calcified, enclosed in a tough fibrous capsule. More often they extend and soften and may then, by haemic invasion, produce a terminal miliary tuberculosis or lead to some other complication, such as paraplegia, acute pneumonic pulmonary tuberculosis, or a cold abscess.

Progress of
forms

5.—CLINICAL PICTURE AND TREATMENT

(1)—Acute Generalized Miliary Tuberculosis

Clinical picture

The clinical manifestations of acute generalized miliary tuberculosis are extremely varied, but three characteristic forms of the disease are sufficiently distinctive to deserve recognition; namely, a typhoidal form in which localizing features are generally absent, a pulmonary form in which pulmonary features predominate from the onset, and a meningeal form in which meningitis is throughout the chief feature.

Typhoidal,
pulmonary,
and
meningeal
forms

Typhoidal
form

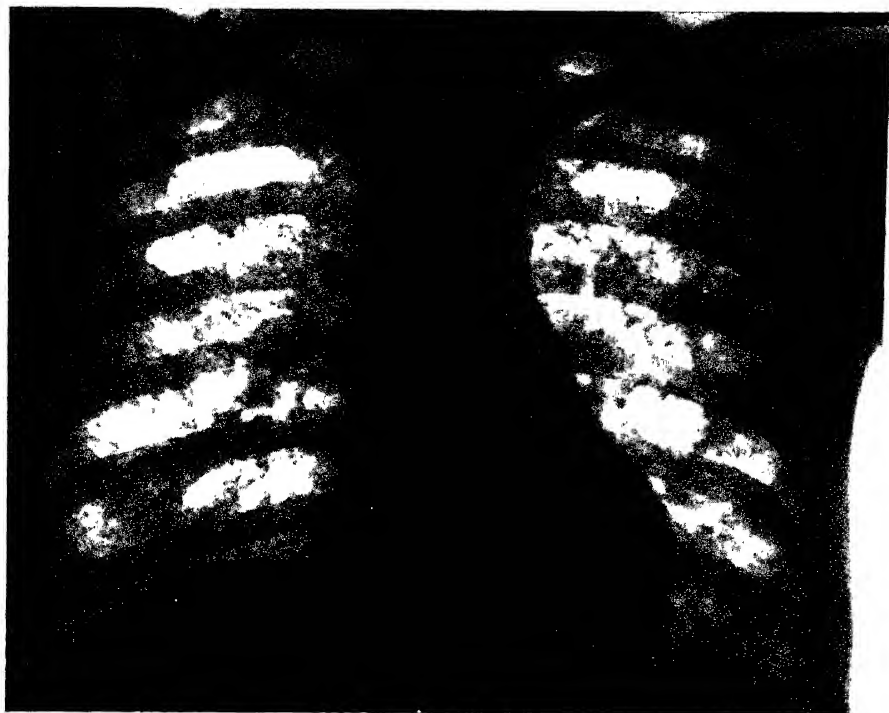
The typhoidal form often begins insidiously with weakness, wasting, and pyrexia, but soon the toxæmia becomes severe. A dry hot skin, cracked tongue, slight cyanosis, rapid loss of weight, tachycardia, and persistent pyrexia are the general features. The spleen is often palpable. As a rule the lungs do not show any changes or only fine bronchitis on clinical examination. With rapid progression of the disease the patient soon sinks into a torpid state and dies in coma usually within six weeks. In the pulmonary form the initial symptoms of toxæmia are accompanied by increasing dyspnoea, cyanosis, and productive cough in a way that points to serious implication of the lungs. These pulmonary symptoms are always disproportionately severe in comparison with any abnormal physical signs in the chest; as a rule there is evidence only of fine bronchitis or patchy collapse, or else of emphysema. Radiography of the chest is essential to determine the true condition by the characteristic fine mottling always seen in the lung fields (see Plate VII, A). The meningeal form of miliary tuberculosis is found when the generalized dissemination of the disease involves the meninges from the start. Its clinical features are described elsewhere (see MENINGITIS, Vol. VIII, p. 499).

Pulmonary
form

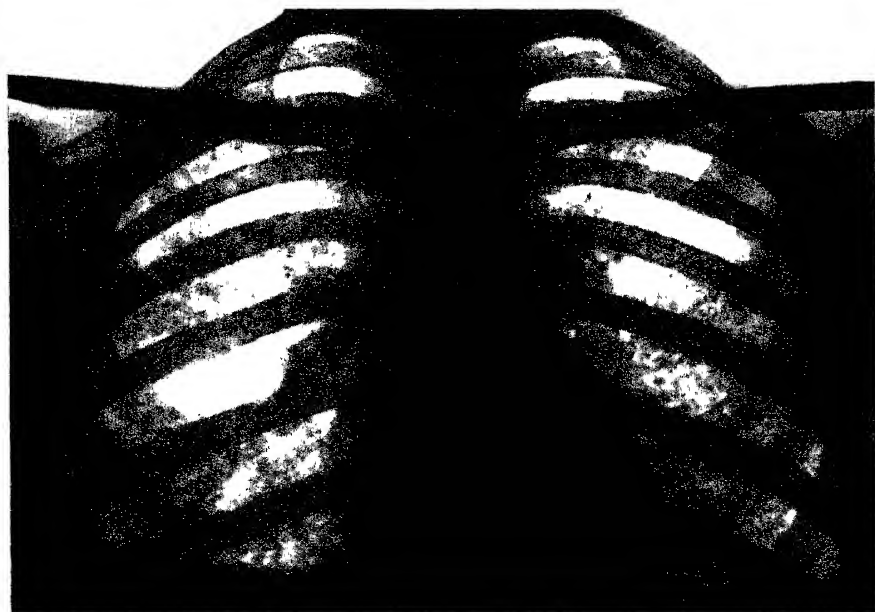
Meningeal
form

Course and
prognosis

Acute generalized miliary tuberculosis is usually fatal within six weeks. A fatal prognosis, however, is not justified now in the early stages or



A



B

A. Radiograph of acute miliary tuberculosis: necropsy control. B. Radiograph of chronic miliary tuberculosis of lungs in a young woman with a caseous tuberculosis of uterus, both Fallopian tubes, and ovaries: necropsy control

PLATE VII

[To face p. 302

from X-ray evidence alone unless the meninges are affected, because there are records of recovery. Although there are a few genuine examples of recovery from tuberculous meningitis this is excessively rare. On the other hand, provided that the meninges escape involvement there is more chance that the disease may become chronic or that recovery may occur. Though it is not known how commonly this happens, it is probably much rarer in infants and children than in adults.

Diagnosis and differential diagnosis

The diagnosis of acute generalized miliary tuberculosis is always difficult and often delayed, especially in the typhoidal form, unless a radiograph of the chest is taken at once whenever the condition is suspected. Enteric fever is excluded by the rapid pulse, the absence of a rising tide of agglutinins, negative blood cultures, and the presence of a polymorphonuclear leucocytosis. Progressive endocarditis is excluded by the absence of a progressive valvular lesion and also negative blood cultures, the latter, of course, also excluding a septicaemia. In the presence of signs of meningitis examination of the cerebrospinal fluid is imperative; the raised pressure, fine cobweb coagulum, reduced chlorides, raised protein, excess of lymphocytes, and perhaps the presence of tubercle bacilli confirm the diagnosis.

There are only a few other conditions that produce radiographs like *Radiography* those of miliary tuberculosis in a patient with an acute illness. A rare form of miliary broncho-pneumonia can do so, though here the lesions are generally coarser and fuse quickly; moreover there is intense cyanosis, irregular pyrexia, copious sputum with a mixed bacterial flora, and a high polymorphonuclear leucocytosis. Miliary carcinomatosis of the lungs runs a course of a few months with symptoms resembling those of miliary tuberculosis; but it is rare, especially before middle life, there is no fever as a rule, but intense dyspnoea, perhaps invasion of the superficial lymphatic glands, and evidence of the primary growth, commonly a gastric carcinoma. Syphilis, psittacosis, and periarteritis nodosa occasionally affect the lungs in a fashion which may be confused with miliary tuberculosis; diagnosis in such rare cases rests upon the general clinical features, the Wassermann reaction, and perhaps biopsy of a superficial nodule in periarteritis.

Bacteriological proof of tuberculosis during life is not easy to obtain though occasionally the organisms are found in the cerebrospinal fluid or stools. Choroidal tubercles if present are diagnostic, but in my experience they are very rarely found.

Treatment

Complete rest in bed is essential and also skilled nursing attention. Medicinal treatment is entirely symptomatic. In the meningeal form lumbar punctures repeated at intervals of a day or two help to relieve the headache, the distressing cry, and the convulsions.

(2)—Chronic and Healed Generalized Miliary Tuberculosis

Incidence

Until recently miliary tuberculosis pursuing a chronic course or healing has been regarded as nothing more than a curiosity of occasional pathological interest. In 1924, however, Burnand and Sayé gave a clinical description of a few examples. Subsequently there has been an increasing recognition of the frequency with which a prolonged course occurs, a recognition which has been furthered greatly by a much wider use of radiology in routine diagnosis of pulmonary disorders. Hoyle and Vaizey recently collected and analysed 110 cases from the literature and added to these 10 others of their own.

Radiography

Miliary tuberculosis pursuing a chronic course is commonest in adolescence and early adult life. It usually arises insidiously with a dry cough, smouldering pyrexia, malaise, and loss of weight. In others the onset is like that of the acute disease. As a rule abnormal signs are few and may be limited to the general features of a toxæmic illness coupled with evidence of localized infiltration of one or both lungs or of a fine bronchitis. The spleen is not uncommonly enlarged and occasionally is enormous. A diffuse lymphadenitis is another important feature. Focal tuberculosis of the skin, genito-urinary tract, a joint, the iris, or more rarely some other organ may also occur. Such lesions may appear concurrently or in a consecutive fashion during the course of the disease. Radiographic examination of the chest is essential for the recognition of the disease, and the miliary shadows then seen are usually numerous, small, discrete, and symmetrical (see Plate VII, B). Their density is sometimes greater than in the acute disease: owing to fibrosis, and they sometimes appear calcified. When there are calcified miliary foci in the spleen or liver they are demonstrable radiologically. In a few the radiographic appearances of the lungs are quite atypical for miliary disease owing to the presence of a latticed pattern in the lung fields and abnormal mediastinal and hilar shadows. This feature occurs in the lymphogenous form of the disease.

Course and prognosis

Cases fatal within six months

Cases fatal after longer period

It is convenient to distinguish three groups of cases of chronic miliary tuberculosis as regards the course and prognosis. One group consists of those in whom the disease ends fatally in less than six months. These patients usually have an abrupt onset; the course is febrile without remission and is commonly terminated by tuberculous meningitis. Here the disease closely resembles acute miliary tuberculosis with a prolonged duration. A second group consists of those with a fatal termination after a course longer than six months and averaging about two years; the onset is more often insidious, there are remissions in which the disease is apparently quiescent for a short time, and there is often clinical evidence of extra-pulmonary focal tuberculosis. Tuberculous meningitis is again the common termination, though sometimes there is a peculiar form of progressive toxæmia with severe emaciation and dyspnoea, cyanosis, and little or no pyrexia. Occasionally the pulmonary lesions produce a cor pulmonale and terminal congestive

heart failure. But some patients recover spontaneously and retain normal health; Hickling recorded two cases in which recovery followed surgical removal of a massively enlarged tuberculous spleen. Apparently after quiescence for two years relapse is infrequent. The pulmonary lesions sometimes remain clinically unimportant throughout the course of the disease; some patients have transient pyrexia, cough, and malaise at the onset but respond rapidly to treatment by rest. In others the disease is never recognized during this active phase and only discovered by chance when already obsolete. Radiologically in this group the lesions may disappear completely or may become steadily more opaque from fibrosis or calcification.

Patients who recover

Diagnosis

A diagnosis of chronic generalized miliary tuberculosis is justified only when there is good evidence that miliary lesions seen in the lungs radiologically are tuberculous, and when there is evidence of generalization of the disease. Many cases of chronic miliary tuberculosis do not show any clinical evidence of generalization and even at necropsy it may be hard to find, the lungs bearing the brunt of the disease. Proof of tuberculosis rests on detection of the organism either in sputum, fasting gastric contents, the urine, the discharge from a sinus, or elsewhere, or upon the histological examination of an excised lymphatic gland or affected piece of skin. Cultures and inoculation of a guinea-pig should be used if necessary. In quiescent or healed cases direct evidence of this kind may not be available during life; the diagnosis must then rest upon probability and exclusion of other conditions.

Chronic generalized form

Detection of organism

The main sources of difficulty are tuberculous broncho-pneumonia, carcinomatosis, and pneumoconiosis. Tuberculous broncho-pneumonia presents a different radiological picture in its earliest phases and a rapid course with cavity formation. It is rare for carcinomatosis to cause confusion and then only in its miliary form in the lungs or as lymphangitis carcinomatosa; these are commoner after fifty years of age, always lead to great dyspnoea but rarely to fever, and end fatally within a few months. The primary growth is most often in the stomach and may provide diagnostic features. Pneumoconiosis is distinguished from chronic miliary tuberculosis by a history of prolonged exposure to harmful dust. Other conditions occasionally causing difficulty in diagnosis are miliary congestion of the lungs, occurring with some underlying cardiovascular lesion and with clinical signs of congestive cardiac failure: fungoid infections, xanthomatosis, Hodgkin's disease, bilharziasis, and Boeck's sarcoid. Confusion with the latter is especially likely in the presence of skin involvement. Diagnosis between the two conditions may be impossible unless tubercle bacilli can be identified, because the histological appearances are not always satisfactory as a means of separating the two diseases. Many believe that sarcoids are a non-caseating form of tuberculosis (Pinner).

Diagnosis from tuberculous broncho-pneumonia
From carcinomatosis

From pneumoconiosis
From other conditions

Treatment

Patients in whom the disease runs a progressive course have no prospect of recovery, and treatment is symptomatic. Those with quiescent lesions do not need any treatment, though periodic observation is a wise precaution. With the intermediate group treatment by prolonged rest in bed offers a prospect of averting a fatal outcome. In some of these, bilateral artificial pneumothorax is worth a trial though severe dyspnoea is a limiting symptom that restricts its use even in favourable cases. Treatment by gold sodium thiosulphate (sanocrysin, crisalbine) or other gold salts is advocated by Sayé; small doses should be used and with great caution.

(3)—Acute Generalized Massive Tuberculosis*Incidence*

This rare form of tuberculosis is seen as a rule during early childhood, or among negroes and other primitive races.

Clinical picture

Acute forms occur as a severe and progressive febrile illness, accompanied generally by rapid wasting, tachycardia, multiple adenitis, and an enlarged spleen. Enlargement of the spleen is common and it may be massive from multiple large caseous foci. The lesions in the lungs are often not shown by abnormal physical signs until they are far advanced. Recurrent dissemination of the bacilli by the blood-stream may be inferred from fresh lesions in the lungs, or by the appearance at intervals of crops of papulo-necrotic tuberculides or, in infants, of subcutaneous nodular tuberculous abscesses. Transient attacks of meningeal or cortical irritation have been described with various neurological signs closely simulating those of tuberculous meningitis and with changes in the cerebrospinal fluid pressure, number of cells, and globulin content. These attacks appear to be due to a small caseating focus in the meninges or cortex.

*Evidences of recurrent dissemination**Course and treatment*

As a rule this form of generalized tuberculosis is fatal within a few weeks. Treatment is limited to the provision of adequate facilities for rest, feeding, nursing care, and the relief of symptoms.

(4)—Chronic Generalized Massive Tuberculosis*Types*

Generalized tuberculosis with lesions that are massive rather than miliary is occasionally chronic. Four types are now sufficiently distinguished to deserve recognition as separate clinical groups, though individuals may sometimes show features of more than one group as the disease extends.

Protracted dissemination

(i) Chronic pulmonary tuberculosis is occasionally accompanied by concurrent or consecutive tuberculous involvement of bones or joints, the genito-urinary system, the skin, or more rarely by lesions elsewhere. Such features are significant of generalization of the disease in Schürmann's sense of protracted dissemination. The clinical features of the individual lesions do not differ in any way from those associated with focal tuberculosis in the various organs affected. (ii) Tuberculous



Radiograph showing hilar lymphadenopathy and disseminated lesions in both lungs of milia. This patient was blind from chronic iridocyclitis and had enlargement of both parotid glands, generalized enlargement of superficial lymph glands and of the spleen. Histological examination of a lymphatic gland showed chronic miliary tuberculosis. (Reproduced by kind permission of Dr. W. D. W. Brooks)

PLATE VIII

polyserositis, polyorrhomenitis, or Concato's disease (see also ASCITES, *Polyserositis* Vol. II, p. 157). (iii) Generalized tuberculosis with massive lesions confined to the lymphatic system was first described by Osler; he found the most extreme examples in negroes, and others have since found the same (Lincoln). The characteristic feature is a more or less general enlargement of lymphatic glands. The retroperitoneal, mesenteric, and bronchial glands are affected especially, but superficial nodes may also become enormously enlarged. The chronic course is sometimes accompanied by little or no evidence of toxæmia for long periods. Sometimes a massive generalized tuberculosis of the entire abdominal glandular system produces a clinical picture closely resembling coeliac disease with chronic wasting, abdominal distension, and bulky pale fatty stools. At other times there is a strong resemblance to Hodgkin's disease. Histological examination of an excised gland will usually decide the diagnosis. (iv) A further group of cases occurs in which the features of this preceding group are accompanied by lesions in other viscera, pointing to hæmic as well as lymphatic dissemination of the disease (see Plate VIII). Thus there may be tuberculous iridocyclitis, uveoparotitis, a massively enlarged caseous spleen, and focal tuberculosis of the spine, genito-urinary tract, skin, or lungs. *Lymphatic type*
Haemic and lymphatic dissemination

The outlook in these forms of generalized tuberculosis is always uncertain and usually poor. Few patients survive for more than a year or two though some remarkable examples are on record in which the lesions have become quiescent and health has been restored. In such cases extensive calcification occurs in the affected organs. Treatment follows the general lines for an active tuberculosis. For those cases included in groups (ii) to (iv) the cautious use of ultra-violet rays or exposure to sunlight may be beneficial. *Prognosis and treatment*

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TUBEROUS SCLEROSIS

See EPILOIA, Vol. V, p. 118

TULARAEMIA

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1.—DEFINITION

(*Synonyms*.—Deer-fly fever; rabbit fever)

1556.] Tularaemia is a specific infective disease due to *Bacterium tularense*. It is wide-spread in nature in various animals, principally rodents, and is acquired by man through handling infected animals or their carcasses, or transmitted to man from infected animals by biting insects.

2.—AETIOLOGY

The first case in man to receive bacteriological proof was reported from Cincinnati in 1914, but the disease is known to have occurred in the United States of America as early as 1907. The causal organism was identified in 1912 during a study of an epidemic among ground squirrels in California and named after the county, Tulare, in which the discovery was made. Francis in 1920 gave a clear account of the disease as it occurs in animals and man and of the methods by which it is transmitted. The disease has been reported to occur in man in the United States, Japan (1925), Russia (1928), Norway (1929), Canada (1930),

*Earliest
reports of
the disease*

*Geographical
distribution*

*Modes of
infection*

Sweden (1931), Austria (1935), Czecho-Slovakia (1936), and Turkey (1936). It is unknown in the British Isles except as a laboratory infection.

It is most commonly acquired through an abrasion of the skin of the hands in those killing or handling the carcasses or skins of infected rabbits or hares, but it may not be possible to discover the site of entry. It is also transmitted from infected animals by biting insects, most commonly the horse-fly (*Chrysops discalis*) and the wood-tick (*Dermacentor andersoni*), but other blood-sucking insects, such as lice, flies, bugs, and ticks may act as the transmitter. It has been acquired by eating partly cooked rabbit, and by the bites of animals whose mouths have been contaminated. The disease has been acquired by man in one or other of these ways from the wild rabbit, hare, tree squirrel, ground squirrel, lemming, guinea-pig, water-rat, wild rat, white rat, ground-hog, skunk, musk-rat, coyote, opossum, fox, deer, quail, and sage-hen, from scratches by a cat, and by picking ticks from a dog. Water has been contaminated and has given rise in Russia to an epidemic in man. Laboratory workers who handle living cultures of the organism or perform necropsies on inoculated animals seldom escape infection. Infection from man to man is unknown.

3.-BACTERIOLOGY AND MORBID ANATOMY

*Causal
organism*

Bacterium tularensense is a small pleomorphic Gram-negative coccobacillus, aerobic, non-mobile, and non-spore-bearing. It grows well on coagulated egg-yolk and blood-glucose-cystine-agar but not on ordinary laboratory media. It has been isolated directly from man on culture media but has not been identified in smears made from human lesions. It is best isolated by the inoculation of guinea-pigs with material from lesions and has been obtained in this way from blood taken from patients during the first week of the disease.

*Histology of
lesions*

In the morbid anatomy of the individual lesions there is a similarity to tuberculosis and two concurrent processes may be recognized, necrosis, and a reaction of reticulo-endothelial-monocyte-epithelioid type. In early lesions necrosis predominates, in late lesions the cellular reaction, and old necrotic lesions become encapsulated by fibrous tissue. It is doubtful if the diagnosis can be made on the histological appearances alone.

*Primary skin
lesion*

The primary skin lesion is a reddened papule that breaks down to form a punched-out sloughing ulcer. If the primary lesion is in the eye, there is infiltration of the conjunctiva by lymphocytes and poly-

Other lesions

morphonuclear leucocytes and foci of caseous necrosis. The regional lymphatic glands are enlarged and may suppurate; a nodular or confluent pneumonia occurs in a large proportion of the fatal cases; the spleen and liver often contain focal lesions and more rarely similar lesions are found in the kidneys, intestines, brain, and meninges. Exudative lesions may occur in the alveoli and peritoneum.

4.—CLINICAL PICTURE

After an incubation period of from one to ten days there is a sudden onset of headache, vomiting, chill, fever, and aching in the back and limbs. Weakness, anorexia, loss of weight, sweating, and prostration follow. Skin eruptions, macular, papular, vesicular, or pustular, may occur at any time in the course of the disease. In the *ulcero-glandular type* that arises from a primary skin lesion there is pain in the regional lymphatic glands for forty-eight hours before an inflamed papule appears at the site of entry. This rapidly becomes pustular; a necrotic plug is discharged and a punched-out ulcer forms. Pneumonia, bronchitis and pleurisy, and meningitis occur as complications of this type. In the *oculo-glandular type*, pain in the eye, photophobia, lacrimation, oedema of the lids, conjunctivitis, and painful enlarged regional lymphatic glands are the characteristic features. A *glandular type* occurs with enlarged regional glands but no primary lesion. A *typhoid type* in which there are general symptoms but no primary lesion and no regional enlargement of lymphatic glands is the form usually found in laboratory infections. In the *ingestion type*, in which the infection arises from imperfectly cooked meat from an infected animal, the onset is marked by vomiting, abdominal pain, and diarrhoea.

5.—COURSE AND PROGNOSIS

In most cases the active stage of the disease lasts for two or three weeks and in the absence of complications recovery is the rule, but the convalescence is often prolonged and complete recovery may be delayed for several months. Recurrences of slight fever with lassitude and weakness may interfere with the capacity for hard work for as long as a year. The course may be greatly prolonged by complications. Suppuration in enlarged lymphatic glands has been recorded at any time from one to twenty-four months after infection.

Recovery is the rule in the *oculo-glandular type*, without permanent impairment of vision. In cases with pulmonary complications the mortality rate is about 40 per cent. Meningitis is usually fatal, and death has occurred in most cases acquired from eating partially cooked meat from infected animals. The total mortality rate is between 4 and 5 per cent. One attack confers lasting immunity.

6.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In cases of the *ulcero-glandular type*, the primary skin lesions and the enlarged regional lymphatic glands make the diagnosis easy in a locality where the disease is common, especially if there is a history of handling

the carcass or skin of a rabbit or other rodent, but tularaemia should be considered as the possible cause of every case of undiagnosed fever in an area where it is known to occur. Cases subsequently proved to be tularaemia have been provisionally diagnosed as influenza, typhoid fever, sporotrichosis, undulant fever, tuberculosis, psittacosis, and septic infections.

- rod counts* The blood count is not characteristic, a mild secondary anaemia being commonly found with a moderate leucopenia or leucocytosis.
- glutinins* Specific agglutinins are present in the serum in the second week of the disease, attain a maximal concentration between the fourth and seventh weeks, and remain present for as many years following infection as observations have been recorded.
- tradermal
ists* Foshay (1932, a) recently prepared a detoxified antigen for intradermal tests that may enable a specific diagnosis to be made in the first week, but the value of this test has still to be accurately defined. The infecting organism has been isolated by inoculation into guinea-pigs of the blood during the first week, and of pus from the primary lesion and from suppurating lymphatic glands.
- olation of
ganism*
- erum*

7.—TREATMENT

No preventive treatment has so far been discovered apart from protection by rubber gloves of the hands of those who dress the carcasses or handle the skins of infected rodents. The treatment of the disease is almost entirely general and symptomatic. The primary skin lesion should be treated by the application of dressings and when supuration occurs in a lymphatic gland it should be incised. Foshay (1932, b) has recently prepared a therapeutic serum from goats, but its value is not yet established.

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TUMOURS

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Reference may also be made to the following title:

CANCER

1.-INTRODUCTION AND DEFINITION

1557.] Though the term tumour, in its widest sense, may be applied clinically to any mass arising within the tissues, it is proposed in the present article to limit the discussion to tumours of a purely neoplastic character. A neoplasm has been defined as 'an autonomous or independent new growth' (Thoma), i.e. a local proliferation of cells not subservient to the needs or control of the body but self-regulating in their powers of growth and spread. The present article is limited to a general consideration of the clinical and morbid features of such growths,

the manner of their spread, and certain effects that they may exert upon the body as a whole.

2.—CLINICAL FEATURES OF BENIGN AND MALIGNANT TUMOURS

From the clinical point of view the most important question that must be answered on discovering a tumour is: 'Is it benign or malignant?' In the minds of many this distinction is apt to be of a mixed clinico-pathological character that eludes precise definition. The purely clinical conception of a benign tumour as harmless to its host, in contradistinction to the malignant tumour that kills, does not take into account the numerous instances in which a histologically benign tumour is fatal by virtue of its position in the body, for example a small polypoid glioma in the aqueduct of Sylvius and myo-adenomas of the prostate (see also p. 321). The histologically benign tumour may thus be clinically malignant. From the pathological aspect, however, benign and malignant tumours are distinguished by a number of histological criteria.

*Characters
of benign
tumour*

When a tumour is readily accessible to the examiner its character may often be decided without much difficulty. The benign tumour is characteristically circumscribed and, in yielding tissues, tends to be spherical. It expands the surrounding structures without becoming fixed to them and therefore, in soft tissues, has a certain amount of mobility. Its growth is slow and if it is removed it does not recur. The malignant tumour often grows rapidly, and rapidity of growth alone should arouse suspicion even if the tumour appears otherwise to be benign. It is not limited by a capsule and it tends to infiltrate the surrounding tissues and hence becomes fixed to them. In addition the examiner may find evidence of metastases in the regional lymph nodes or even in more remote parts of the body.

*Characters
of malignant
tumour*

Although these elementary but fundamental distinctions are applicable in most instances, the clinician may at times be deceived by them. A tumour macroscopically benign in appearance may be malignant, for example in some carcinomas of the thyroid there are metastases from what would otherwise be dismissed as an innocent adenoma. Again malignant changes, only revealed by the microscope, may take place in an apparently benign tumour, for example sarcomatous transformation in a fibromyoma of the uterus. The converse may also be true: a poorly defined, non-encapsulated growth may yet be clinically benign, for example most melanomas of the skin and certain lipomas of the subcutis. The demonstration of metastasis, however, is generally accepted as unimpeachable evidence of malignancy except perhaps in the central nervous system, where metastatic spread by the cerebro-spinal fluid may take place from a histologically benign tumour such as naevilloma of the choroid plexus (Van Wagenen).

3.—MORBID ANATOMY

(1)—Macroscopic Features

Many tumours, however, are revealed only at operation and it is therefore important to recognize the macroscopic features of malignant growths. These may be summarized as follows.

Infiltration or invasion by tumour of surrounding tissues independently of lined channels

The growth, either on superficial examination or on section, or on both, is ill-defined. Its borders are irregular and, when presenting on a free surface, often raised and everted. The adjacent tissues of the host are penetrated by tongues or fine anastomosing strands resembling the substance of the main tumour in colour and texture. Such infiltration causes the tissues to become abnormally firm or indurated, a factor of considerable diagnostic value when the primary growth is diffuse and ill-defined—for example in the stomach. When serous surfaces are involved they are often puckered, the area resembling a scar.

Induration

Permeation

The lumina of blood-vessels, ducts, and lymphatics may become occupied by tumour cells in continuity with the main growth. Thus a carcinoma of the kidney may block the lumen of the renal vein and extend thence into the inferior vena cava. Lymphatic permeation, for example in the peritoneum or pleura, is often clearly shown by distension of the vessels with opaque greyish-white tumour tissue which causes them to stand out sharply against the background.

Metastasis

Cells or groups of cells are detached from the primary tumour and are carried as emboli by the lymph- or blood-stream to distant sites where they come to rest and, by proliferation, form a secondary growth. Metastasis may also take place first by the lymphatics and secondly, after traversing the thoracic duct, by the blood-stream. Frequent sites of such secondary growths are the lymphatic glands, liver, lungs, bones, and brain. Voluntary and cardiac muscle and the spleen are very rarely affected, from which it would appear that the nature of the soil must be an important factor in controlling dissemination. Macroscopically these secondary deposits appear on the surface of a viscus, such as the liver, as firm, slightly raised or flat, greyish-white, sharply-defined areas. They may be haemorrhagic or have haemorrhagic borders. In the larger foci there is often a depressed or umbilicated centre due to central necrosis. Lymph nodes occupied by secondary growth are often enlarged and unusually firm: their superficial and cut surfaces are altered in colour and texture by the replacement of their normal tissue by growth, which is most often firm and greyish-white.

Spread by lymph- and blood-streams

Appearances of metastases

Spread by gravity

By physiological propulsion

By cerebrospinal fluid

By transplantation

By artificial inoculation

Metastasis may also be promoted by other forces, such as gravity: for example secondary deposits from a carcinoma of the stomach may be found in the pelvic peritoneum. Physiological propulsion is often quoted as an agent but its action is very questionable. It is, however, possible that tumours are disseminated from a higher to a lower part of the intestinal tract by peristalsis, but in such instances it is difficult to disprove that spread has taken place through lymphatic permeation. The circulation of the cerebrospinal fluid is responsible for the dissemination of certain tumours of the central nervous system when these are so placed that their cells have access to the fluid (Cairns and Russell). Malignant tumours are spread by this means more often than benign. A rarer method of spread is transplantation by apposition, for example in carcinoma of the lip. Artificial inoculation of tumour by the surgeon's knife is now very rare. Kettle recorded a case in which exploratory needling of a carcinomatous liver was followed by a secondary deposit in the abdominal wall. This possibility should not be forgotten in view of the renewed enthusiasm in recent years for biopsy by needling, for example in carcinoma of the breast.

(2)—Microscopic Features

In many instances the naked-eye features of a tumour are indecisive and microscopic examination is necessary to determine whether it is benign or malignant. In such an examination the following points must be taken into consideration.

Character of the growth as a whole, whether typical or atypical

Typical growths

In general benign growths are typical, i.e. they resemble fairly closely the tissue of origin both in the morphology of the individual cells and in the manner in which they are arranged. A good example is the adenomatous polyp of the intestinal mucosa. The resemblance between the cells of a benign tumour and the parent tissue may even extend to function; thus the cells of an adenoma of the liver may secrete bile. Tumours of the endocrine glands often display this propensity to such an extent that the body as a whole is affected by their activity (see p. 321). But malignant tumours may also, though more rarely, reflect the functions of the tissue of origin; thus carcinomas of the intestinal tract are often composed of mucus-secreting cells and the metastases from such tumours are generally of a similar character. Von Eiselsberg's classical case is often quoted, in which myxoedema followed the surgical removal of a carcinomatous thyroid gland, was relieved later upon the appearance of a functioning secondary deposit in the sternum, but reappeared when this was excised. The myxoedema, however, failed to improve when, still later, another metastasis appeared in the scapula.

Atypical growths

In contrast to the benign, the malignant tumour departs from the cell-morphology and architecture of the tissue of origin to a greater but still variable extent. In general, the greater the departure the more

malignant is the tumour. When a tumour closely resembles in structure the tissue of origin it is said to be highly differentiated; in losing these distinguishing characters it becomes dedifferentiated, and finally undifferentiated. The process by which such dedifferentiation takes place is referred to as anaplasia. In different phraseology the cells are said to revert to a more embryonic type. *Differentiation*
Anaplasia

The recognition of anaplasia is of the greatest importance in diagnosis and prognosis. Upon it depends the system of grading of tumours introduced by Broders (1920), based upon his observations on a large series of cases of epithelioma of the lip. According to this system individual cases were placed in one of four grades according to the relative proportions of differentiated and undifferentiated tumour tissue in the excised specimen. Grade 1 comprised tumours in which three-quarters of the tissue showed differentiation; grade 2 showed equal proportions of differentiated and undifferentiated tissue; grade 3 showed differentiation in one quarter of the tissue only, and in grade 4 there was no tendency towards differentiation. In 1925 Broders revised his system slightly so that a somewhat larger number of tumours would be placed in the two lower grades. His work has met with considerable support, especially in the United States, as an aid in prognosis and in following up cases. *Broders' grading of tumours*

Although its application to relatively small growths such as epithelioma of the lip, which are completely excised and can be examined microscopically with relative thoroughness, is undoubtedly sound and useful, it is doubtful if the system can be used in other classes of tumour. It is a common experience that in dealing with a large solid tumour, whether carcinomatous or sarcomatous, there is much variation in both architecture and cellular differentiation in different areas. To assign such a tumour to its correct grade would involve immense labour since a complete histological examination of the whole mass would be obligatory. Also it is well known that a tumour upon which an operation has been performed may undergo anaplastic changes in a short space of time. I have examined gliomas which, on surgical removal, have displayed a highly differentiated cellular structure but which, although the extirpation appeared to be complete at the time, have recurred within a year or eighteen months and have been found, on re-examination, to exhibit extreme dedifferentiation. In the light of such experience prognosis is rendered exceedingly difficult. Finally certain tumours, although well differentiated, possess a surprising degree of malignancy, for example the colloidal adenocarcinomas of the thyroid which retain a remarkably typical structure even in the metastases. Again the histological distinction between chondromas and chondrosarcomas is often extremely difficult, the appearance of the latter being misleadingly typical. Any attempt to grade such tumours according to Broders' standards would be futile and of little prognostic value. According to Boyd, grading by microscopical criteria should not take the place of careful clinical judgement, nor should the prognosis *Limitations of Broders' system of grading*

be based slavishly upon it. He considers that the value of grading lies rather in the help given in assessing the radiosensitivity of the tumour.

These criticisms should not be interpreted as a reactionary effort to belittle this work. That closer attention to the structural details of tumours will be rewarded is indicated by such studies as those of Callender and Wilder, who analysed a series of forty-six cases of choroidal melanoma followed for five years and showed that metastasis had not occurred when argentophil fibres were present throughout the tumour; when, however, these fibres were absent in some areas metastasis occurred in 68 per cent of cases; and when fibres were entirely absent all the patients had died.

Invasion

Capsule

Further evidence of the nature of a tumour may be sought in the character of its boundaries. The benign tumour is characteristically circumscribed and often enclosed by a capsule formed as the result of pressure upon the adjacent tissues of the host. Such pressure leads to degeneration and a gradual disappearance of the cells at the periphery, while the residual supporting connective-tissue becomes condensed to form a collagenous sheath around the tumour. In malignant tumours such a capsule is usually absent, the margins showing areas in which the tumour is actively invading the surrounding tissues. Such invasion

Method of invasion

is manifested by the extension of narrow trabeculae or broader tongues of tumour cells beyond the limits of the main mass. Extension tends to take place along lines of least resistance, for example in the loose connective-tissue separating muscle bundles or epithelial structures and along the perineural sheaths of nerves. In the course of such invasion lined channels such as lymphatics and blood-vessels may be occupied by tumour cells with subsequent permeation. Such histological features afford clear and incontrovertible evidence of malignancy. In many instances, however, it is necessary to search for earlier stages, and here the relation of the tumour cells to adjacent basement membranes is of the first importance. The existence in a tumour of otherwise benign appearance of any area in which the cells have lost their orderly arrangement and have broken through the basement membrane into the surrounding stroma indicates early malignancy. Such tumours are often designated as precancerous.

Perforation of basement membrane: precancerous stage

Morphology of the cells

Loss of special characters

The divergence in character of a tumour from its tissue of origin with consequent dedifferentiation implies not only the loss of typical architecture but changes in the individual cells whereby they tend to lose any special features that were distinctive of their ancestors. They thus become simplified and, if encountered as a metastasis in another part of the body, may offer no clue to their origin. There is also generally considerable variation in the size of the cells, some perhaps being of giant proportions. Such giant cells may contain one or more nuclei;

Giant cells

in the latter event the nuclei may be superimposed or may be arranged in an annular fashion at the periphery of the cytoplasm. The nuclei of the giant cells vary in size and in their chromatin content. The presence or absence of mitoses is an important indication of the rate of growth of the tumour at the time of its removal. Multipolar mitoses and mitoses in which the number of chromosomes is either increased or decreased are often seen in highly malignant tumours. Such abnormal mitoses are probably closely linked up with the formation of multinucleate giant cells. Multipolar mitoses, however, are occasionally seen in inflammatory conditions and sometimes in tissue-culture preparations of normal tissues. In the latter they are generally ascribed to toxic alterations in the culture medium.

*Mitoses**Abnormal mitoses*

Metastasis

The regional lymph nodes should invariably be examined for the presence of secondary deposits when this is possible, for their demonstration is positive proof of malignancy. Generally the histological character of the deposits resembles closely that of the primary growth both in architecture and in the morphology of the cells. Occasionally, however, the secondary deposits show further dedifferentiation or, perhaps more rarely, the converse. A fully documented and critical survey of the phenomenon of metastasis and other methods of tumour spread is given by Willis.

Examination of regional lymph nodes

(3)—Value of Microscopic Criteria

These elementary histological criteria of malignancy have been briefly stated in order that their relative value in diagnosis may be discussed. With the exception of metastasis none alone provides a certain answer in all circumstances to the question whether the tumour is malignant. The investigation of regional lymph nodes in biopsy specimens is often impossible. Moreover a negative result does not preclude malignancy because metastasis may have taken place by the blood-stream.

Metastasis

Evidence of invasion alone cannot be accepted as indicative of malignancy. It is well known for example that meningiomas often invade the medullary spaces of the adjacent skull and penetrate the large dural sinuses, and may even reach the soft tissues superficial to the skull: I have seen two examples in which the temporal muscles were so affected. Yet these tumours offer no other evidence of malignancy and are clinically benign. The same is true of chromophobe adenomas of the pituitary; although macroscopically apparently circumscribed they often invade the adjacent brain and dura, and even the bony walls of the sella turcica. In other respects they are histologically and clinically benign. The so-called 'cancroid' of the appendix is another instance of a tumour that is locally invasive but rarely gives rise to metastases.

Anomalies of invasion

Moreover in biopsy the borders of a tumour may not be available for examination. In such circumstances the estimation of the degree to which the tumour departs in histological character from the tissue of

Examination of cells

Mitoses

origin is of the greatest importance; and here the loss of normal architecture may be regarded as of greater significance than the presence of morphological variations amongst the individual cells. Abundant mitoses indicate rapidity of growth and, though alone of no great significance, in conjunction with other features should be accepted as supporting evidence of malignancy.

(4)—Association between Benign and Malignant Tumours

It is commonly taught, especially by clinicians, that benign tumours are apt to undergo malignant transformation. In fact this change appears to be uncommon: a benign tumour tends to remain benign, a malignant tumour generally bears this character from the start. Exceptions may be enumerated, and the possibility of this occurrence must always be remembered especially when a benign tumour of long standing manifests rapid growth. An important example is melanoma of the skin. Leiomyomas may become sarcomatous, a change often referred to by clinicians as 'degenerative' although its character is rather of the reverse order. In most carcinomas of the thyroid the growth is largely adenomatous. When multiple adenomas of the intestinal tract, especially of the stomach, occur carcinomatous transformation may take place in only one of them. The same is true of villous papillomas of the bladder and the skin papillomas of tar-workers. Sarcomatous change may, though rarely, occur in neurofibromas of the peripheral nerves; I have recently seen such an example in neurofibromatosis.

*Melanoma**Leiomyomas**Adenomas of
thyroid and
stomach**Papillomas**Neuro-
fibromas*

4.—LATENT PRIMARY TUMOURS

Many instances might be quoted of tumours that have given no hint of their presence until the results of erosion have led to the sudden perforation of a viscus or blood-vessel, with catastrophic results. It is by no means uncommon for a primary tumour to remain hidden and symptomless and for the patient to seek medical help on account of the effects of one or more metastatic deposits. Examples of this nature are fully and systematically discussed by Willis, and a few only of the commoner instances will be mentioned here.

*Latent
carcinoma
of stomach**Latent
carcinoma
of lung*

Latent carcinoma of the stomach may be accompanied by hepatic enlargement from multiple metastases; by bilateral (Krukenberg) tumours of the ovaries resulting from trans-peritoneal metastasis; or by metastatic deposits in the recto-uterine pouch which may mimic a primary stenosing carcinoma of the rectum. Instances of latent primary carcinoma of the lung with metastasis in the brain are remarkably common. Necropsy in such cases may fail to reveal deposits in other tissues and, unless an exhaustive search is made throughout the lungs, the cerebral focus may be mistaken for the primary tumour. Radio-graphy of the chest during life may enable a correct diagnosis to be

made, but many of these tumours are too small or, if bronchogenic, too diffuse to be readily identified by this means. The prostate, breast, kidney, and testis may also be mentioned as not uncommon sites of a latent primary carcinoma. *Other sites of latent growths*

5.—EFFECTS OF TUMOURS ON THE BODY

(1)—Benign

Serious consequences may follow the development of a benign tumour by reason of its position. Such consequences may initially be purely local, for example the production of internal hydrocephalus by a colloid cyst blocking the foramen of Monro, and of hydronephrosis by a papilloma of the ureter. The problem in each instance is anatomical. It is proposed here to consider briefly more remote effects of pressure or obstruction due to a benign tumour, attributable to some chemical change, hormonal or otherwise, within the body fluids.

Obstruction

A common example in which both local and remote effects may easily be traced is in diffuse enlargement of the prostate due to multiple myo-adenomas. Such an enlargement, especially when the middle lobe is affected, causes urethral obstruction as a result of which the bladder undergoes dilatation and hypertrophy, shared by the ureters and pelves of the kidneys. In such circumstances infection of the urine readily occurs leading to cystitis and an ascending pyelonephritis. Renal function is thus impaired and evidence of uraemia may be found on clinical examination, constituting a dangerous and often fatal complication. A somewhat parallel course of events might be traced in cases in which a benign tumour of the papilla of Vater causes obstruction to the flow of bile with resulting jaundice and cholangitis. *Enlargement of prostate*
Tumour of papilla of Vater

Hormonal effects of endocrine tumours

In a different category, and of peculiar interest, are the hormonal effects upon the body of benign, and more rarely of malignant, tumours of the endocrine glands. These are described fully under the titles of the various glands. Mention may, however, be made here of the hyperinsulinism caused by an islet adenoma of the pancreas, recognition of which has led to the surgical removal of the tumour and the cure of the patient in a number of cases (Fraser, Maclay, and Mann). Another example is the clinical syndrome of pain and tenderness in the bones, spontaneous fractures, and a raised serum calcium due to hyperparathyroidism. Pathologically a generalized osteitis fibrosa with the formation of osteoclastomas and bone cysts is associated with one or more tumours of the parathyroid glands. Turnbull considered that such tumours were the result of functional hyperplasia and was disinclined to regard them as autonomous new growths (Hunter and *Islet adenoma of the pancreas*
Tumour of the parathyroid

*Adenoma of
pituitary*

*Cushing's
syndrome*

*Chorion-
carcinoma*

Turnbull). Acidophil adenomas of the pituitary give rise to gigantism and acromegaly, and basophil adenomas have been associated by Cushing with the well known syndrome that bears his name. But the recognition of Cushing's syndrome in association also with adenoma of the adrenal cortex and, more rarely, with carcinoma of the thymus presents a problem that as yet has eluded analysis. It appears likely that chemical investigation of the hormonal substances present both in the tumour tissue and in the urine will constitute the next advance. Of interest also in this connexion is the urinary excretion of gonadotropic hormone giving a strongly positive Zondek-Aschheim reaction in patients with chorion-carcinoma.

Remote effects of pressure

*Chromophobe
adenomas of
pituitary*

*Suprasellar
tumours*

*Fröhlich's
syndrome*

*Tumour of
pineal body*

Of different pathogenesis are certain syndromes that arise through pressure-effects of benign tumours in the region of the hypothalamus and pituitary. The basophil and acidophil adenomas of the pituitary are, as already mentioned, associated with striking physical changes in remote parts of the body. Tumours of the chromophobe cells of the pituitary cause other changes, not by reason of any specific hormonal effect but by destruction of the anterior lobe by pressure. This occurs because these tumours usually attain a relatively large size in comparison with the chromophil adenomas. The clinical manifestations are those of hypopituitarism, namely a gradually acquired obesity, variable degree of loss of hair, wrinkling and loss of elasticity of the skin, and depression of sexual function. A somewhat similar, though exaggerated, picture may accompany suprasellar tumours but here, through involvement of the hypothalamus, there may be in addition polyuria, increased sugar tolerance, hypersomnia and, if the subject is a child, stunting of growth. When obesity is pronounced the term Fröhlich's syndrome, or dystrophia adiposo-genitalis, is often given to the condition. That this syndrome is referable to pressure upon the hypothalamus is proved by its development also in cases of gross internal hydrocephalus.

A somewhat similar mechanism appears to be responsible for the occurrence of pubertas praecox in association with tumours of the pineal body and of the hinder part of the hypothalamus.

(2)—Malignant

General

Cachexia

One of the commonest effects upon the body of malignant disease is progressive wasting ultimately reaching a state of cachexia. So characteristic is this that any history of an unexplained substantial loss in weight should immediately raise the suspicion of cancer. The means whereby such an effect is exercised are not clear. Contributory factors are undoubtedly loss of appetite and an inability on the part of the intestinal tract to digest fully the food consumed. Another factor is the increased break-down of protein in the body. This is associated, in advanced cachexia, with albuminuria and excretion of acetone and

aceto-acetic acid. At necropsy, in addition to the general wasting, there is brown atrophy of the heart, liver, and thyroid gland.

Blood

It has long been known that immature cells may appear in the peripheral blood in advanced stages of cancer. A more precise description has recently been published by Vaughan under the title 'leuco-erythroblastic anaemia' which she defined as an anaemia in which immature red cells and a few immature white cells of the myeloid series are present in the peripheral blood. The degree of anaemia is variable, ranging in her series from 2,200,000 to 5,300,000 red cells per c.mm. A similar anaemia may be found in certain other conditions but it is characteristic of a carcinomatosis in which the bone marrow is the seat of metastatic deposits. Conversely, however, extensive carcinomatosis of the bones may be unaccompanied by leuco-erythroblastic anaemia. Moreover there appears to be no intimate relation between this anaemia and the site of the primary growth, the length of the history, the degree of skeletal involvement, or calcium metabolism. Macroscopically there is a great increase of the red marrow of the bones, this red marrow being found in sites which normally, for the age of the patient, should be occupied by fatty marrow only. Obviously therefore the anaemia is not dependent upon depletion of the haemopoietic marrow by the metastases. Microscopically the marrow characteristically contains unusually large numbers of immature red cells. No explanation has been offered of the way in which the anaemia is produced. Treatment with iron or with liver extracts has been ineffective; it appears therefore that it is not due to a deficiency of these factors.

Leuco-erythroblastic anaemia

Changes in marrow

Cause of the anaemia

Effects upon body fluids

The hypothesis that cancer is responsible for some specific change in the body fluids has been the basis of a number of so-called cancer tests. These have received considerable publicity and not uncommonly forms of treatment have been evolved from them. Thus Abderhalden's test was instituted for the diagnosis of pregnancy and later extended as a test for disease in general and cancer in particular. It depended upon the presence of specific ferments in the blood in different conditions. The specificity of the ferments, however, was subsequently disproved. More recently a test has been introduced by Bendien who claimed that in a cancerous subject the fraction of serum proteins precipitated by a sodium vanadate-acetic acid solution and dissolved in sodium bicarbonate solution gave a characteristic ultra-violet absorption curve. These tests, and others including the Freund-Kaminer test, have been investigated by groups of workers at the London Hospital and none has proved reliable. The results of these investigations have been reviewed collectively by Pantou. At the present time no substance has been identified in the body fluids of cancerous patients

Abderhalden's test

Bendien's test

Evaluation of tests

upon which may be based either a reliable diagnosis or any effective treatment.

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TYMPANITES

See AEROPHAGY, Vol. I, p. 257; and
DYSPEPSIA, CARBOHYDRATE INTESTINAL, Vol. IV, p. 372

TYPHOID FEVER

See ENTERIC FEVERS, Vol. V, p. 50

TYPHUS FEVERS

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Reference may also be made to the following title:

ARTHROPODS AND DISEASE

1.-FEVERS OF THE TYPHUS GROUP

Definition

1558.] Till recently the name typhus fever has been used only as a designation for an epidemic continued fever of a clear-cut clinical and epidemiological type. Within the past few years three other distinct forms of disease have come to be recognized as belonging to the same group as historical typhus, differing sharply from that disease in being primarily diseases of lower animals which are not conveyed from man to man but from animals to man by ticks, mites, or fleas. In their clinical features, causal organisms, and pathology they are very closely related to epidemic typhus but, being epizootic diseases which are only incidentally conveyed to man, they are non-epidemic sporadic place diseases. A brief survey of these diseases and their relation to epidemic typhus is an essential preliminary to a clear understanding of the whole group of typhus fevers.

Extensive and intensive research is in progress on the non-epidemic typhus fevers and a number of points remain to be cleared up, but it is already possible to give a simple provisional classification which will enable the practitioner to obtain a good working knowledge of their diagnosis and management. Research workers tend to magnify minor points of distinction between these various fevers which are observed in different parts of the world, with the result that no fewer than fifty names have been given to the tick-, flea-, and mite-borne typhus fevers and much confusion has been caused.

*Rocky
Mountain
spotted fever
and 'Japanese
river fever'*

Two of the non-epidemic fevers which are now generally accepted as members of the typhus group have been well known for many years, namely, the spotted fever of the Rocky Mountains and the Japanese river fever. Both these fevers were known to resemble epidemic typhus in their clinical characters but, being sporadic place-diseases associated with life in the open country rather than with conditions of poverty and overcrowding, it was natural that great hesitation should be felt in grouping them with classical typhus. It was only when their causal micro-organisms and the morbid changes in the tissues were found to be very similar that their close relation to typhus was admitted. In 1936 a third type of non-epidemic flea-borne typhus, usually called murine or endemic typhus (see p. 337), was discovered. The general features of the epidemic and non-epidemic typhus fevers are shown in the following table which is intended for the practitioner rather than the research worker. Their geographical distribution is shown in Plate IX.

*Murine
typhus*

EPIDEMIC		NON-EPIDEMIC OR EPIZOOTIC			
Communicated from man to man by lice. Associated with famine, filth, and overcrowding		Sporadic place-diseases, communicated from lower animals to man by various arthropods. Mostly diseases of the open country. Not associated with famine, filth, overcrowding, or lice			
	LOUSE-TYPHUS	FLEA-TYPHUS	TICK-TYPHUS	MITE-TYPHUS	
varieties	Typhus fever, typhus exanthematicus	Murine typhus, endemic typhus, urban tropical typhus	Rocky Mountain spotted fever, <i>Fièvre boutonneuse</i> , tick-bite fever, Indian tick typhus	Tsutsugamushi, Japanese river fever, scrub tropical typhus, Sumatra mite-fever	
distribution	- Cosmopolitan. Less common in the tropics	Many localities all over the world	Many localities in America, Europe, Africa, and Asia	Oriental tropical and subtropical countries	
causative agents	- <i>Rickettsia prowazekii</i> - Human lice especially <i>Pediculus humanus corporis</i>	<i>R. mooseri</i> (or <i>R. murina</i>) Fleas (especially <i>Xenopsylla cheopis</i>)	<i>R. rickettsi</i> (or <i>R. conori</i>) Various kinds of ticks especially <i>Dermacentor andersoni</i> and <i>Rhipicephalus sanguineus</i>	<i>R. tsutsugamushi</i> (or <i>orientalis</i>) Mites (<i>Trombicula akamushi</i> and <i>T. deliensis</i>)	
animal reservoirs of infection	Man	Rats and mice	Rodents of the wilds; possibly dogs and other domestic animals	Rats and mice	
serum agglutination, response to	<div> <div>OX 19 + + +</div> <div>OX K -</div> </div>	<div> <div>+ + to + + +</div> <div>- to ±</div> </div>	<div> <div>±, +, or + +</div> <div>-, ±, +, or + +</div> </div>	<div> <div>- to ±</div> <div>+ + to + + +</div> </div>	
rash					
macular or papular, often faint. Rare on palms, soles, and face	- Macular or papular, often faint. Rare on palms, soles, and face	As in louse-typhus but often faint or absent	Macular or papular, common on palms, soles, and face	Macular or papular, often on face, rare on palms and soles	
local sore, lymphangitis and lymphadenitis	Nil	Nil	Rare in Rocky Mountain typhus, and Indian tick-typhus: common in <i>Fièvre boutonneuse</i> and other African tick-typhus fevers	Almost constant in Japanese mite-typhus: often absent in mite-typhus of Malaya and Dutch East Indies	
mortality	5 to 50 per cent	0 to 4 per cent	1 to 70 per cent	1 to 60 per cent	
cross immunity in animal experiments					
Immunizes against	Flea-typhus	Louse-typhus	Nil	Nil	
Does not immunize against	Tick-typhus except S. African	Tick-typhus	Louse- or mite-typhus. <i>Boutonneuse</i> fever does not immunize against Rocky Mountain tick-typhus	Any other typhus fever	

	EPIDEMIC		NON-EPIDEMIC OR EPIZOOTIC			
	Communicated from man to man by lice. Associated with famine, filth, and overcrowding		Sporadic place-diseases, communicated from lower animals to man by various arthropods. Mostly diseases of the open country. Not associated with famine, filth, overcrowding, or lice			
	LOUSE-TYPHUS		FLEA-TYPHUS	TICK-TYPHUS	MITE-TYPHUS	
Scrotal reaction in guinea-pigs	Rare (only in 2 to 20 per cent)		Common in murine typhus; slight or absent in Malayan flea-typhus	+++ in virulent Rocky Mountain tick-typhus; - to ± in <i>boutonneuse</i> and very mild Rocky Mountain tick-typhus	- to ± except in the Queensland mite-typhus in which it is + to ++	
Inoculability of rats	± (dies out after 2 to 3 passages)		+ to +++	- to ± in <i>boutonneuse</i> fever	- to + in Japanese mite-typhus; + to ++ in other mite-typhus fevers	

The classification adopted in the table does not claim to be final, but the principles on which it was based when I proposed it in 1921 are now widely accepted. These were (i) that the name 'typhus' should be applied to all the fevers of the group as this provides a helpful suggestion to the practitioner who encounters a continued fever with the general characters of a typhus fever, and (ii) that the name of the arthropod vector concerned should be applied, as this indicates the chief epidemiological feature of the disease. An important later modification consisted in the division of the fevers of the typhus group into two main classes, namely, epidemic and non-epidemic typhus fevers, with the intention of emphasizing the essential difference between epidemic louse-borne typhus, the virus of which is directly communicated from man to man, and the non-epidemic fevers conveyed by ticks, mites, and fleas, which are primarily diseases of the lower animals and are sporadic place-diseases communicated from animals to man by their respective vectors. Louse-borne typhus is a disease of poverty, overcrowding, and louse-infestation, whereas the non-epidemic typhus fevers are diseases of persons living in association with the animals which form the reservoirs of infection, usually in the open country. The practitioner will sometimes be unable to determine whether in a given case of non-epidemic typhus the vector is a tick, mite, or flea; but if, as is usually the case, he can decide that the fever is conveyed by one or other of these three arthropods and not by lice he will be relieved of the great load of responsibility which would have rested on him if the case had been one of louse-borne typhus.

Epidemic and non-epidemic typhus fevers

Mexican and Manchurian typhus

A reservation must be made in the case of the Mexican flea-borne typhus fever (*tabardillo*) which in its severe form has a mortality of 20 to 40 per cent and is believed to be transmissible by both fleas and lice. The Manchurian flea-borne typhus, though usually mild, is also believed to be transmissible by fleas and lice. These two forms of flea-borne

typhus differ so strikingly from the many other local forms found all over the world that they represent a difficult problem. At present they should be classed as louse-borne epidemic typhus from the point of view of their practical management.

The table shows the great variability in the serum reactions in tick typhus and in the results of animal inoculations with the various kinds of virus. These variations may, to some extent, be accounted for by differences in virulence of the infecting organisms but they also suggest that undue reliance cannot be placed on such tests as scrotoal reactions in guinea-pigs or the susceptibility of experimental animals. *Animal inoculation*

The point on which the practitioner can and must have clear ideas is the transmissibility or non-transmissibility of the infection from man to man in natural conditions. With regard to this there can be little doubt except in the ambiguous cases of Mexican and Manchurian typhus, for of all the thousands of cases of non-epidemic typhus fevers which have been under treatment there is no record that infection has been conveyed from the patient to the attendants, despite the fact that many patients have been treated before the relation of the disease to epidemic typhus was suspected. General clinical and epidemiological investigation must still play a very important part in connexion with the typhus fevers, though it is certain that fuller knowledge of their experimental characters will eventually solve the remaining problems connected with them. *Transmission from man to man*

2.—EPIDEMIC OR LOUSE-BORNE TYPHUS FEVER

(*Synonyms*.—Typhus fever; typhus exanthematicus; camp fever; jail fever; famine fever)

(1)—Definition and History

1559.] Louse-typhus is an epidemic continued fever caused by a rickettsia body, *Rickettsia prowazeki*, which is conveyed from man to man by human lice.

Epidemic typhus fever is a disease of great antiquity; some of the cases of epidemic fever described by Hippocrates were undoubtedly typhus. The earliest clear account of the disease was written in 1546 by Fracastorius who described a 'febris pestilens' which prevailed in Italy in 1508 and 1528 and on each occasion followed a great famine. Since that time there have been many accounts of great epidemics of the disease in Europe and the British Isles, chiefly in times of famine. Numerous outbreaks have been described in military camps, jails, ships, and law courts. In some epidemics a large proportion of the population of the affected areas suffered from the disease. Although some of the accounts of epidemics are vivid descriptions of typhus, others are ambiguous because of the coexistence of typhoid fever, relapsing fever, or plague which were not differentiated from typhus till about a hundred years ago. *Earliest accounts*

The name typhus came into use about 1800; until then the disease had *Nomenclature*

passed under many different names; Murchison (1873) gave a list of about 100 synonyms. Some of the names indicated the contagiousness of the disease, others its epidemic nature or its prevalence in camps, prisons, hospitals, ships, or in time of famine. Many of the titles referred to the eruption or to the 'malignancy' and 'putridity' of the disease. Since 1837, when Stillé and Gerhard independently showed that typhoid fever was a separate disease, the names typhus fever and typhus exanthematicus have been almost universally adopted.

In 1844 Henderson differentiated relapsing fever from typhus. In 1862 Murchison emphasized the contagiousness of the disease, but believed that the disease was caused by a poison generated from time to time *de novo* in the exhalations of living human beings by overcrowding and bad ventilation. In 1868 Hallier of Jena claimed to have cultivated the 'contagion' on the cut surface of a lemon on which he had smeared the blood from a typhus patient. The growth which he obtained was a fungus, *Rhizopus nigricans*. The interest of this experiment was that it showed how some observers, even then, were groping for the parasite of the disease.

First attempt
to cultivate
organism

In 1909 C. Nicolle produced the disease in a chimpanzee by subcutaneous inoculation of blood from a patient, and in the same year he, with Comte and Conseil, transmitted the disease to monkeys by the bites of lice which had fed on an infected chimpanzee. In 1910 Ricketts and Wilder described pleomorphic organisms in the bodies of infected lice; these organisms were studied later by Prowazek and da Rocha-Lima (1916), and were accurately described by the latter who called them *Rickettsia prowazeki*.

First
transmission
to animals

Isolation of
organisms

In 1910 W. J. Wilson found that certain bacteria of the *coli* group which he had isolated from typhus patients were agglutinated by highly diluted sera of patients with the disease, but he disclaimed any suggestion that the serum response proved the bacteria to be the cause of the disease.

Weil-Felix
reaction

In 1916 Weil and Felix, using a different organism (*Bacillus proteus* X 19) which had also been isolated from typhus patients, worked out the test known by their names. The name 'Wilson-Weil-Felix' would seem a more appropriate title as the principle on which the reaction is based was first discovered by Wilson.

(2)—Aetiology

Geographical
distribution

The geographical distribution is much the same as that of relapsing fever except that epidemic typhus does not so readily establish itself in tropical countries (see Plate IX). Over large areas in India and tropical Africa great epidemics of relapsing fever have occurred, but louse-borne typhus has not been recorded. The distribution of the disease is much more restricted than formerly; most of the countries of Western Europe and the United States, which were formerly visited by frequent epidemics, are now entirely free from epidemic typhus. The disease is liable to become epidemic in any country which has a louse-infested

population and a fairly long cool season. Epidemics have occurred during recent years in eastern Europe, especially in Poland, Russia, Ukraine, and Rumania. In Africa, Egypt, South Africa, Algeria, Morocco, and Tunis have had severe outbreaks; in Asia, Siberia, Corea, Manchuria, northern China, and Asia Minor have had outbreaks; in America, Mexico, Bolivia, and Peru have reported numerous cases. Lesser outbreaks have occurred in many subtropical and temperate regions. During and after the War 1914-18 extensive epidemics ravaged most of the countries of eastern Europe.

Most of the cases in the northern hemisphere occur between October and June; the disease usually dies down during the hot season when louse infestation is low and the opportunities for transmission of the virus are relatively few. *Seasonal prevalence*

Both sexes and all ages are equally susceptible, although children may seem to be immune because in them the disease is mild. *Age and sex incidence*

(3)—Bacteriology and Morbid Anatomy

The virus is now generally accepted as *Rickettsia prowazeki*; it is conveyed from man to man by the human louse, *Pediculus humanus*, especially the body louse, *P. humanus corporis*, which seems to be a more effective vector than *P. humanus capitis*. The virus is present in the blood and organs during the acute stages of the disease, and to a lesser extent during convalescence, but it soon ceases to be transmissible by lice even though it is believed to persist for long periods in the bodies of persons who have suffered from the disease. *Causal organism and vector*

Lice which have fed on infected persons are incapable of conveying the disease by their bites for 8 to 10 days, but thereafter remain infective for the rest of their lives. The rickettsia bodies multiply exceedingly in the epithelial cells of the mid-gut of the infected louse. It is doubtful if lice are able to transmit the virus to their offspring. The maintenance of infection during periods between epidemics is probably by means of mild 'inapparent' attacks, especially in children. *Cycle in the louse*

Rickettsia bodies are also found in small numbers in the endothelial cells of the small blood-vessels of persons who have died of the disease. They are pleomorphic, resembling small bacteria or cocci, stain with Giemsa's stain, and are Gram-negative. They do not grow on ordinary media but multiply rapidly in tissue cultures and in live chick-embryos.

Monkeys are susceptible to the virus, so also are guinea-pigs in which the virus can be maintained for many generations though the disease is mild and scrotal reactions are absent or slight unless the animals have been devitalized in some way. The virus cannot be maintained in rats for more than two or three generations although rats are very susceptible to most of the strains of *Rickettsia* found in the non-epidemic forms of typhus. *Susceptibility of animals*

Some workers believe that the rickettsia bodies are developmental stages in the life history of *Proteus X 19*, but this view is not generally accepted despite the apparent specificity of the Weil-Felix reaction. *Relation to Proteus X 19*

Mode of infection

European workers have failed to transmit the virus by any vector other than the human louse and have been unable to discover infection in rats or other animals during epidemics. Some experts believe that the virus of the epidemic typhus of Mexico and Manchuria can also be conveyed by fleas from man to rats and from rats to man, but in the rest of the world the evidence points strongly to the louse as the sole vector. Lice are believed to convey infection either directly by their bites or by depositing infected faeces on the skin; in the latter event the virus would enter the body through the wound made by the insect in biting or more probably through an abrasion. Several workers have died of typhus contracted in the course of their experiments with infected lice.

Immunity

One attack confers immunity, but this gradually wears off and second attacks after intervals of a few years have been recorded; these are usually milder than first attacks. According to some workers the immunity consists of 'premunization' due to the persistence of the virus in the body for long periods after the attack.

Morbid anatomy

The characteristic lesions are minute nodules in the walls of the small blood-vessels of the brain, kidneys, and other organs, consisting of collections of mononuclear leucocytes and more or less necrosed endothelial cells of the blood-vessels. This necrosis of the blood-vessels is believed to be the cause of the haemorrhages which occur in severe cases.

(4)—Clinical Picture and Course

Incubation period

Epidemic typhus varies in severity from mild 'inapparent' attacks to severe and rapidly fatal forms. The incubation period is usually from 8 to 14 days, the extremes being 4 and 20 days. It tends to be longer in mild attacks and shorter in severe cases.

Onset

The onset is usually rapid or sudden, with chills or rigors and frontal headache. Pains in the back and limbs are common. Vomiting occurs in 25 to 50 per cent of the cases. The symptoms steadily increase with the rise of the temperature to its maximum of 102 to 105° F. which is reached within 36 to 48 hours as a rule. After 3 or 4 days the face becomes dusky and flushed and the conjunctivae are injected. Insomnia occurs in 50 per cent of cases and may be accompanied by slight delirium. A dry cough is common at this stage. The onset differs chiefly from that of enteric fever in its greater rapidity and in the earlier appearance of nervous symptoms. By the end of the fourth or fifth day the patient may already be in the 'typhoid state'.

Rash

In most cases the rash appears on the fourth or fifth day but it may be delayed till the sixth or seventh. Small rose-red papules or macules are first seen on the sides of the chest, soon spreading to the rest of the trunk and to the limbs. The spots are numerous, fade on pressure at first, but soon become deep red and then brownish and cease to disappear on pressure. In severe cases the spots often have a haemorrhagic point at their centre surrounded by a brown mottling. By the tenth to

the twelfth day the spots begin to fade, leaving a brownish discoloration which may persist for some days or even for two weeks. The eruption varies greatly in appearance. In mild cases, especially in pigmented skins, it may be difficult to detect, even on careful examination; in severe cases groups of haemorrhagic spots may coalesce to form purpuric patches. A point of diagnostic importance is that the spots seldom appear on the face, palms, or soles.

Some of the many types of temperature curve are shown in Fig. 22. *Temperature curve*
The commonest type shows a rapid rise followed by a period of con-

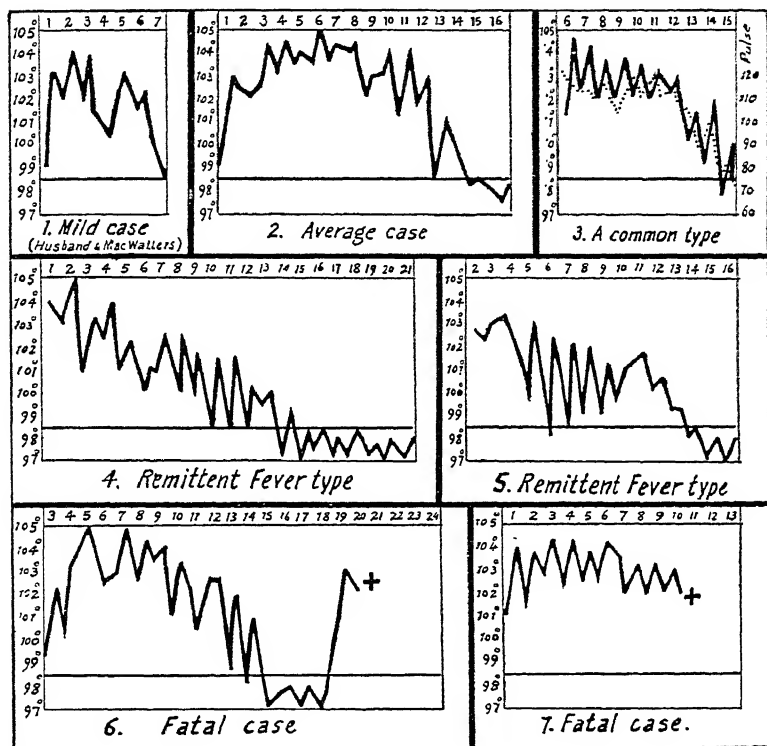


FIG. 22.—Temperature charts in louse-typhus. (This and Fig. 23 from *Tropical Diseases*, by Rogers, L., and Megaw, J.)

tinued fever lasting about a week in which there may be remissions of two or even three degrees. By the tenth to the thirteenth day the temperature begins to fall by crisis or rapid lysis. The total duration of the fever is usually 12 to 16 days, but in very mild cases it may be as short as a week and in these cases the fever may be deeply remittent or even intermittent.

The pulse is rapid at first but soon becomes slower than would be expected from the height of the temperature. A low blood-pressure and tendency to heart failure are important features, not only towards the end of the febrile period but also during early convalescence. A moderate degree of leucocytosis is usual, but there may be leucopenia. *Circulatory system*

<i>Blood and spleen</i>	The red blood-cells may exceed five millions per cubic millimetre and the haemoglobin may exceed 100 per cent. The spleen is palpable in about 25 per cent of cases.
<i>Gastro-intestinal symptoms</i>	The tongue is coated and often dry; sordes appear on the lips and teeth. Constipation is usual but there may be diarrhoea especially towards the crisis, 'critical diarrhoea'. Tympanites is not so common as in enteric fever. Apart from occasional febrile albuminuria the kidneys are little affected in mild cases, but in fulminant cases there may be severe haemorrhagic nephritis. Early frontal headache is often followed by delirium which may be of the low muttering type or noisy and violent. Insomnia, apathy, and drowsiness are common and may appear within the first two or three days. Slight bronchitis often occurs and broncho-pneumonia is one of the common causes of death.
<i>Kidneys</i>	
<i>Nervous system</i>	
<i>Respiratory system</i>	
<i>Other features</i>	Thrombosis of the femoral vein is an occasional complication. Gangrene of the toes has been reported in 1 to 4 per cent of the cases. Parotitis occurs in 2 to 4 per cent of cases and is sometimes suppurative. Bed-sores are common in severe cases when the nursing arrangements are bad.

(5)—Prognosis

<i>Mortality</i>	The death-rate varies greatly in different epidemics. In an average type of outbreak affecting people of all ages the mortality ranges from 10 to 20 per cent, but in virulent outbreaks, among famine-stricken people, it may be 50 per cent or higher. In fatal cases death usually occurs from the eighth to the fifteenth day, and more patients die on the eleventh day than on any other. Age is a very important factor; for example in an epidemic with a total mortality of 15 per cent the death-rates at various ages will be approximately: under 5 years 5 per cent, between 5 and 10 years 4 per cent, between 10 and 20 years 3.5 per cent, and between 20 and 30 years 10 per cent; from the age of 30 it rises progressively so that by the age of 60 it may be 50 per cent and it reaches 70 or 80 per cent in patients over 65. The early appearance of delirium or stupor, a haemorrhagic eruption or other haemorrhages, broncho-pneumonia, and thrombosis of the large veins are unfavourable features.
<i>Influence of age</i>	
<i>Unfavourable features</i>	

(6)—Diagnosis and Differential Diagnosis

During an established epidemic there will seldom be any difficulty in diagnosis, but the earliest cases are often overlooked. All cases of fever with sudden onset occurring in a louse-infested community should be regarded with suspicion and treated as cases of typhus until the cause of the fever has been satisfactorily explained or until typhus can be excluded. Before the appearance of the rash there is no criterion by which a definite diagnosis can be made but it is most important that suspicion should be aroused at the earliest possible moment so that steps may be taken to prevent the spread of infection. The presence of lice and the history of contact with other cases are important evidence.

The Weil-Felix test is of great value but it may not be positive till about the tenth day. The test, however, should be carried out as early as possible as a rise in the titre of the reaction is a valuable indication; for example a titre which rises from 1 in 20 to 1 in 100 is far more significant than one which remains constantly at the level of 1 in 100. A reliable *O* strain of *Proteus X 19* must be used, and reactions of less than 1 in 200 should not be regarded as diagnostic unless the titre of the response has risen greatly from the onset. By the twelfth to the sixteenth day or so the reaction will often have become positive in dilutions of 1 in 1,000 or more. During convalescence the response gradually becomes more feeble, so that the reaction may be negative in the third or fourth week of convalescence.

Weil-Felix test

Flea-borne typhus may resemble mild epidemic typhus so closely that a differential diagnosis may be impossible unless the epidemiological features of the case give a clear indication. Not only may the symptoms be the same, but the Weil-Felix reaction also gives the same results in both cases. Evidence of contact with other cases of epidemic typhus may clear up the difficulty, but doubtful cases should be assumed to be louse-borne typhus and suitable precautions taken.

Diagnosis from flea-borne typhus

Tick-typhus may also be very like louse-typhus, but the character of the rash and its distribution are different; the circumstances usually leave no doubt, as tick-typhus is essentially a disease of the open country and louse infestation is usually absent.

From tick-borne typhus

From enteric fever the diagnosis is by blood-culture, the characters of the rash, and the serum-reactions. A source of error is that in persons who have been inoculated with T.A.B. vaccine the titre of the Widal reaction often rises steadily even in cases of typhus fever.

From enteric fever

(7)—Treatment

Preventive

This is on exactly the same lines as in louse-borne relapsing fever (see Vol. X, p. 591). Thorough delousing of all patients and contacts invariably proves successful in stamping out the disease. Preventive inoculation by several different methods has been employed on a large scale. Weigl thoroughly tested a method which involves the cultivation of the virus in lice. He worked out an ingenious method of inoculating the insects per rectum by the introduction of capillary tubes containing the virus. By feeding the insects on blood introduced in the same way large quantities of rickettsia bodies are obtained. The mid-guts of the infected lice are separated and emulsified in a weak carbolic acid solution. This killed vaccine has considerable protective power but is expensive and not obtainable on the open market. The method is specially valuable in the protection of research workers, doctors, and attendants on the sick.

Vaccine

Weigl's method

Blanc vaccinated many thousand persons in French Morocco with the live virus of flea-borne 'murine typhus'. Guinea-pigs are inoculated with this virus and killed after the full development of the infection; their organs are emulsified and treated with ox bile to attenuate the

Blanc's method

virus. From a single guinea-pig one thousand doses of live attenuated vaccine can be obtained; this must be used at once for mass inoculation. Excellent results have been obtained, but rather severe reactions follow in a considerable proportion of European subjects though in very few of the indigenous population. As a few fatalities have been reported, the method cannot be regarded as free from risk. The vaccine appears to produce a mild, usually inapparent, attack of flea-borne typhus which protects against the closely related virus of louse-borne typhus.

Several other methods of protective inoculation have been tried but are not yet available for general use. Delousing must still be considered the best and safest method of prevention.

Curative

Convalescent serum

There is no reliable specific treatment for epidemic typhus fever. The serum of convalescents has been used in doses of 20 to 50 c.c. subcutaneously, with some degree of success, but great care is needed in the selection of a donor lest the cure should be worse than the disease. Some work has been done on the preparation of a curative serum from animals, but this has not yet reached the stage at which the treatment is available for general use.

General

The important points in treatment are complete rest in a well ventilated room, light nourishing diet, plenty of water to drink, and careful nursing. Otherwise the treatment is symptomatic. Morphine and small doses of brandy are considered useful by some physicians who have great experience of the disease.

Symptomatic

Delousing

It is very important that the patient should be thoroughly deloused at the earliest possible moment, and that his clothing and bedding should be disinfected. In many cases in which these precautions have not been taken, doctors, nurses, and other attendants have become infected and many valuable lives thus lost.

(8)—Brill's Disease

Historical

This is a mild form of typhus about which there has been much controversy since it was first described by Brill of New York in 1898. Brill recognized the resemblance of the disease to mild forms of classical typhus, but as the disease was strictly sporadic and was never communicated from man to man he concluded that it was a new and different disease. In 1912 it was found that inoculation with the virus of this disease protected animals against the virus of epidemic typhus and so it came to be regarded as an inter-epidemic form of epidemic typhus. In 1926 Maxcy suggested that the disease was conveyed by fleas and when Nicolle in 1933 described '*typhus murin*' as a flea-borne form of typhus it was naturally assumed that Brill's disease was of the same nature, and it came to be regarded as a form of 'endemic' or flea-borne typhus.

Relation to epidemic typhus

Zinsser showed that the virus of Brill's disease is essentially the same as that of epidemic typhus and that nearly all the attacks occurred in persons who had originally come from some European country in

which epidemic typhus was common. It is therefore impossible to doubt that the disease is a late recrudescence of an old attack of epidemic typhus, the virus having persisted in the bodies of the patients for indefinite periods, often ten to twenty years or more. Although 500 cases have occurred in New York alone since 1910 there has been no case in which the infection has been communicated to other persons so that the virus must have lost its power to infect lice.

The name Brill's disease should be restricted to late recrudescences of attacks of epidemic louse-borne typhus and should not be used as a synonym for flea-borne 'endemic' typhus. From the point of view of the practitioner there is little difference between Brill's disease and flea-borne typhus; both are mild diseases and both are incapable of being transmitted directly from man to man by lice. Brill's disease must often occur in countries where epidemic typhus is common as there is no reason to believe that late recrudescences of louse-typhus are restricted to immigrants to the U.S.A.

Definition

*Resemblance
to flea-borne
typhus*

3.—NON-EPIDEMIC OR EPIZOOTIC TYPHUS FEVERS

1560.] These are primarily diseases of animals and are only incidentally conveyed to man by ticks, mites, and fleas. The table on pages 327 and 328 shows the relation of these diseases to epidemic typhus.

(1)—Flea-Typhus

(*Synonyms*.—Murine typhus; endemic typhus; urban tropical typhus; shop typhus; X 19 tropical typhus; Hone's disease; ship typhus)

(a) *Definition and History*

The disease is one of the non-epidemic typhus fevers and is caused by *Rickettsia mooseri* (more suitably named *R. murina*). The virus is conveyed to man from infected rats or other rodents by fleas (*Xenopsylla cheopis*).

In 1926 Maxcy suggested that the sporadic typhus-like fever of North America was conveyed by fleas from infected rats to man. In 1931 Dyer and others conveyed infection from rats caught in infected areas to guinea-pigs by rat-fleas. In 1933 Nicolle described *typhus murin*, a fever occurring in French warships in the Mediterranean, and held that the infection was conveyed from infected rats to man by rat-fleas.

Although the disease has been so recently identified it has already been found to be endemic in many parts of the world. Several diseases which had been previously described as fevers of unknown aetiology are now known to be flea-borne typhus; these include the urban form of tropical typhus, the endemic typhus of North America, and Hone's disease.

The name 'flea-typhus' is suggested as being preferable to 'murine typhus' or 'endemic typhus'; all the non-epidemic typhus fevers are endemic diseases, and mite-typhus is also murine. The only objection that can be raised to the name 'flea-typhus' is that it may be regarded as implying that the virus can never in any circumstances be conveyed

History

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in other ways than by the flea. So long as it is understood that no dogmatic assertion of this kind is involved in the use of the name it seems to be the most appropriate yet suggested.

(b) *Aetiology*

The disease is endemic in many countries all over the world (see Plate IX). The best known foci are in the countries round the Mediterranean, the eastern States of the U.S.A., South Africa, the Malay Peninsula, the Dutch East Indies, Mexico, and Manchuria. Other foci are known to exist in South America, Russia, Australia, India, and elsewhere and it is probable that the distribution of the disease will be found to be almost world-wide.

(c) *Bacteriology and Morbid Anatomy*

*Virus and
vector*

The disease is primarily an epizootic of rats and mice, possibly also of other rodents. Its cause is *Rickettsia mooseri*, which is very closely related to *R. prowazeki*. The virus is conveyed from rat to rat and from rat to man by *Xenopsylla cheopis*, possibly also by other fleas.

*Relation of
virus to R.
prowazeki*

In localities in which the disease occurs it is usually found that a number of rats harbour the virus. The virus differs from that of epidemic typhus in causing a mild disease which is not communicable from man to man by lice, and in causing a disease in rats which is communicable to other rats and to man by rat-fleas. The virus differs from *R. prowazeki* in certain other experimental features but it is similar in the serological response. Some workers believe that *R. murina* is the ancestral form of *R. prowazeki* which for unknown reasons has become modified and capable of being transmitted from man to man by lice. Nicolle, on the other hand, regarded the louse virus as the ancestral strain. One important difficulty remains to be cleared up; Mooser and others hold that the typhus of Mexico (*tabardillo*) and the typhus of Manchuria are capable of being conveyed by both fleas and lice, but flea-borne typhus in all other parts of the world behaves consistently as a purely non-epidemic disease which is not communicable from man to man and is essentially epizootic. Some workers believe that the infection is often, or even usually, conveyed from rats to man by direct contact with rats or by ingestion of food contaminated by the infected urine of rats.

*Morbid
anatomy*

Little is known of the morbid changes in human tissues as the disease is rarely fatal in man, but the lesions in infected animals are very similar to those caused by *R. prowazeki*.

(d) *Clinical Picture*

This differs in no important respect from that of mild forms of epidemic typhus. The onset and course of the fever, the rash, and the Weil-Felix response are essentially similar though, as would be expected from the mildness of the fever, the rash is often faint and may be invisible in dark skins or even in Europeans. The severe manifestations which are common in louse-borne typhus occur only in the exceptionally virulent cases of flea-borne typhus.

(e) Prognosis

The mortality ranges from 0 to 4 per cent except in the case of the Mortality Mexican *tabardillo* in which it may be as high as 40 per cent, but the true nature of this disease is problematical.

(f) Diagnosis and Differential Diagnosis

The occurrence of mild sporadic typhus-like fevers in the absence of louse infestation should suggest at once one of the non-epidemic typhus fevers; if there is also a strongly positive Weil-Felix response to *Proteus OX 19* and a negative response to *OX K*, the probability of the disease being flea-typhus is greatly increased. The final differentiation from the other non-epidemic typhus fevers will depend partly on the character and distribution of the rash and on the epidemiological conditions in which the infection has been acquired, especially the presence of infected rats in the locality and the association of the patient with rats. Animal experiments may be helpful, but even experts often find it difficult to decide which of the viruses of non-epidemic fever is responsible for a particular case.

Diagnosis from other non-epidemic typhus fevers

There is no clinical criterion by which a diagnosis can be made between flea-typhus and Brill's disease but, as the latter form of typhus is confined to persons who have lived in countries where epidemic typhus has occurred, difficulty seldom arises. Inoculation of rats will usually settle the question as they are very susceptible to flea-typhus and are resistant to the virus of Brill's disease.

From Brill's disease

(g) Treatment

Rat destruction is the most important method of prophylaxis. Curative treatment is on the same lines as that of epidemic typhus, except that when the diagnosis of flea-typhus has been established there is no need to take elaborate precautions to prevent the spread of infection to persons who come into contact with the patient or to institute general delousing of the population. In all cases of doubt, and in severe outbreaks of a problematic nature, such as *tabardillo*, strict precautions are essential.

Preventive Curative

(2)—Tick-Typhus

(*Synonyms*.—Spotted fever of the Rocky Mountains; Rocky Mountain fever of the Eastern type; *fièvre boutonneuse*; *fièvre éruptive*; *fièvre exanthématique*; Marseilles fever; *Fièvre escharo noularis*; *dothièndermie aiguë*; tick-bite fever; typhus of São Paulo; typhus of Minas Geraes; Indian tick-typhus)

Probably several strains of virus are concerned in the causation of tick-borne typhus in various parts of the world, but the clinical and epidemiological features of the different forms of the tick-borne disease have so much in common that they can best be dealt with as variants of one disease rather than as independent entities. More than twenty different names have been used to designate tick-borne typhus but, as all these

Nomenclature

diseases belong to the typhus group and all are conveyed by ticks, it is appropriate to call them 'tick-typhus' and to indicate any variations in type which occur by some suitable additional name. The spotted fever of the Rocky Mountains was recognized long before any of the other forms; it has been very thoroughly investigated and can appropriately be regarded as the standard form of the disease. The other types can be most easily understood by considering the respects in which they differ from Rocky Mountain fever.

(a) *Rocky Mountain Tick-Typhus*

(*Synonyms*.—Spotted fever of the Rocky Mountains; Rocky Mountain fever of the Eastern type)

- Definition* This non-epidemic typhus fever is primarily a disease of lower animals, chiefly wild rodents. It is caused by *Rickettsia rickettsi* which is conveyed from animals to man by several kinds of ticks of which the chief are *Dermacentor andersoni*, *D. variabilis*, and *Haemophysalis leporis-palustris*.
- History* The disease has been known for many years in certain areas in the Rocky Mountains. In 1904 Wilson and Chowning found that it was conveyed from its reservoir in wild rodents to man by ticks. In 1909 Ricketts discovered the causal rickettsia bodies in infected ticks. The pathology of the disease was described by Wilson and Chowning in 1902 and was more completely worked out by Wolbach from 1918 to 1922. Other workers who have made important additions to the knowledge of the disease include R. R. Parker, R. R. Spencer, and W. W. King. The following description of the disease is largely based on the writings of R. R. Parker.
- Geographical distribution* Till recently the disease was regarded as restricted to the Rocky Mountain and Pacific Coast States of the U.S.A. Later it was detected in Dakota and since 1931 has been reported from no less than 26 of the central and eastern States. Probably it occurs in nearly all the states of the U.S.A. (see Plate IX). It is essentially a place disease, the distribution of which depends on the presence of infected animals and ticks. In some areas it disappears for a number of years and reappears when conditions again become favourable to its occurrence.
- Seasonal distribution* In the Rocky Mountains most of the cases occur in April and May when the vector ticks are most active; at higher altitudes and in the eastern States most of the cases occur in the summer.
- Epidemiology* Most of the cases occur in out-door workers whose occupation brings them into association with ticks, but some cases have been observed in town-dwellers who have probably become infected by ticks which have been transported by dogs from endemic areas.

Bacteriology and morbid anatomy

The causal organism, *R. rickettsi*, is closely related to *R. prowazeki*. Rodents are the usual reservoirs of infection but small carnivores may also be infected.

The virus is conveyed from animal to animal by larval or nymph ticks. *Transmission* Human beings become infected by the bites of infected ticks, usually adults, as the larvae and nymphs feed chiefly on smaller animals. The part played by large domestic animals and dogs is not clear, for although they are somewhat susceptible to infection it seems likely that their chief role is in bringing ticks which had already been infected into association with human beings. An important practical point is that the virus is inactive in ticks which have been starved for considerable periods and only becomes reactivated a few hours after the tick has had a blood feed either on man or some other animal. A strange feature of the disease is that naturally infected animals have never been discovered; presumably the virus rapidly disappears from infected animals, but during the short period in which it is present all the ticks on the animal become infected.

In addition to hereditary transmission it has been proved that the virus *Transmission among ticks* can be transferred from one tick to another by copulation. In endemic areas only a small proportion of the tick population is infected, often less than 1 per cent and seldom more than 5 per cent. It has also been found that areas in which ticks are infected in one season may be entirely free from infected ticks in the next season.

When a tick has fed on an infected animal it is incapable of conveying infection until about five days have elapsed. The virus gradually becomes greatly concentrated in the tick so that sometimes a single infected tick may contain no less than 15,000 infecting doses. When once the nymphs are infected they remain so for the rest of their lives and also transmit the infection to their offspring.

The infection is usually conveyed to man by the bite of the tick, but the virus can penetrate the unbroken skin and in many recorded cases the disease was probably contracted by picking ticks off dogs or other animals. In this event the virus may possibly enter through the conjunctiva which becomes infected by contact with the fingers. *Transmission from vector to man*

The rickettsia bodies are found in enormous numbers in infected ticks and in much smaller numbers in the tissues of men and infected animals. The lesions caused by *R. rickettsi* are of the same kind as those caused by *R. prowazeki* and the appearance and cultural characters of the two kinds of rickettsiae are very similar. The chief differences are: (i) *R. rickettsi* invades the nuclei of infected cells whereas *R. prowazeki* is confined to the cytoplasm, and (ii) *R. rickettsi* causes a much more severe disease in guinea-pigs and rabbits in which there is usually a pronounced inflammation of the scrotum ('scrotal reaction'). This difference is by no means absolute as blood taken from mild cases may not cause a scrotal reaction in guinea-pigs. Most animals are susceptible but in the larger domestic animals the disease is often 'inapparent'. *The virus*

In all essential respects the morbid anatomy is very similar to that of epidemic typhus. *Morbid anatomy*

Clinical picture and course

incubation
period
local lesion

The general features of the disease are remarkably similar to those of epidemic typhus. The incubation period is from 2 to 14 days, being longer in mild than in severe cases. There is seldom any lesion at the site of the bite, and it may be impossible to find any evidence that a tick has bitten the patient. Occasionally there is enlargement of the

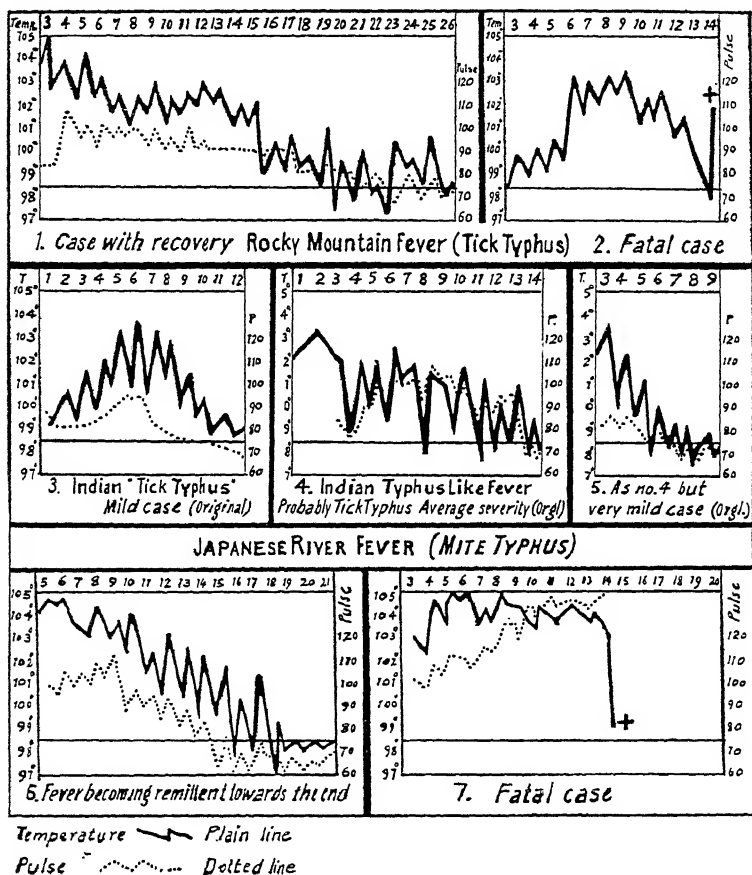


FIG. 23.—Temperature charts in tick-typhus and mite-typhus

lymph glands associated with the site of the bite and rarely there may be a small necrotic area where the tick was attached. Attacks of the usual type have the following features. There may be prodromal symptoms for a day or two before the onset, which is sudden with frontal and occipital headache, lumbar pain, and malaise. Other symptoms which may occur at the onset are chills, sweating, conjunctival injection, pains all over the body, epistaxis, nausea, and vomiting. The temperature rises rapidly to 103° or 104° F., the maximum being reached within three days (see Fig. 23). During this time the symptoms are steadily increasing in severity; the face is becoming dusky

Onset

Temperature

and the eyes are assuming a heavy look. In severe cases the pulse soon becomes feeble and rapid but usually it is slower than would be expected from the height of the temperature. Enlargement of the spleen, cyanosis, and a peculiar odour are early symptoms in some cases, especially in virulent attacks.

The rash appears from the third to the sixth day, usually on the third or fourth. It is first seen on the wrists and ankles and extends rapidly all over the body including the palms, soles, and face. The spots are macules or papules which are rose-red and fade on pressure at first; but they soon become dark and cease to fade on pressure. The spots are sometimes large and scanty, sometimes small and abundant; in the latter case the outlook is less favourable. When the spots darken rapidly or become haemorrhagic the attack is likely to be severe. *Rash*

The course of the fever varies; usually the temperature reaches the maximum in three days and then remains high for about a week; it falls by rapid lysis, reaching normal in four or five days, but sometimes six to eight days elapse before it becomes normal. The total duration of the fever is usually two or three weeks. Moderate remissions often occur throughout the febrile period but are more pronounced during and just before the lysis. Restlessness and insomnia are usual and there may be stupor or delirium. Coma, convulsions, ankle-clonus, Babinski's sign, and Kernig's sign may be observed in some cases. The tongue is coated but red at the edges; constipation is usual but diarrhoea may occur in severe cases, and so may jaundice and enlargement of the liver. The urine is scanty and albuminous in severe cases. There is usually a moderate leucocytosis; total white-cell counts above 20,000 have been seen but generally the leucocyte count is not more than 15,000. There may even be leucopenia; there is usually a relative increase in the lymphocytes. *Course of the fever*
Nervous system
Alimentary system
Urine
Blood

The most common complications are bronchitis, pneumonia, phlebitis, and haemorrhages from the nose, kidneys, and intestines. Iritis and nephritis may occur. Convalescence is usually slow even after relatively mild attacks. *Complications*

The following clinical forms occur: (i) mild ambulatory cases lasting one or two weeks with low remittent or continued fever and a scanty rash; (ii) abortive attacks with sudden onset and rapid rise of temperature to 103° or 104° F., an increased pulse-rate, and a fleeting rash; the symptoms rapidly subside and the attack is over in less than a week; (iii) typical attacks described above, much the commonest form; and (iv) fulminating attacks proving fatal in three to six days, sometimes before there has been time for the rash to appear, but there may be a haemorrhagic rash. The nervous symptoms are severe from the outset and the pulse is very rapid. *Clinical types*

The severity of the disease varies greatly in different localities. The mortality may be many times higher in one place than in another only a few miles away. Even in the same locality the mortality may be low in one year and high in the next. The death-rate may be as low as 5 per *Prognosis*

cent or as high as 50 per cent. The unfavourable features have already been mentioned.

Diagnosis and differential diagnosis

When the disease occurs in localities where it is known to exist mistakes are few, but judging from the extent to which the disease has escaped detection till recently in places where it is now known to be endemic the element of suspicion is obviously important to diagnosis.

Weil-Felix test

In places where other forms of typhus do not occur the Weil-Felix test is of great value, but positive reactions in significant titres cannot be expected till towards the end of the fever. It is very important to have a reliable strain of *Proteus OX 19* and to use freshly-drawn blood. According to Parker reactions in dilutions of less than 1 in 320 cannot be relied on. A steadily rising titre is specially significant. In some cases a positive reaction is not obtained till convalescence has set in. Sometimes the reaction to *Proteus OX K* or *OX 2* may occur in higher titres than the reaction to *OX 19*, and according to Felix the reaction in this and other forms of tick-typhus is only a group-reaction, whereas the reaction to *OX 19* in louse-typhus and flea-typhus and the reaction to *OX K* in mite-typhus are truly specific; Felix considered that a proteus organism specific for tick-typhus might yet be found.

Animal tests

Animal tests are not very helpful in mild cases as the scrotal reaction in guinea-pigs may be fleeting or absent. Immunity tests in animals demand expert knowledge and are not likely to help the practitioner owing to the time which is needed to obtain results.

Diagnosis from epidemic typhus

From flea-borne typhus

Diagnosis from epidemic typhus is usually easy owing to the sharp differences in the conditions in which infection occurs. The character and distribution of the rash is often helpful. When flea-typhus is also prevalent there may be considerable difficulty in distinguishing between mild cases of the tick-borne disease and average cases of the flea-borne disease. The table on pages 327 and 328 shows the general differences between this and the other forms of typhus.

Treatment

Preventive

Areas known to be infected should obviously be avoided; if this is impossible, tick-proof clothing should be worn and the body should be carefully examined for ticks at intervals of five or six hours during the time of exposure to risk; attached ticks should be removed at once and a drop of iodine solution should be applied to the spot. A vaccine has been prepared by making emulsions of heavily infected ticks in dilute carbolic acid. The vaccine gives complete protection against a virus of low virulence and reduces the severity of the disease in cases of infection with highly virulent strains of rickettsiae.

Vaccine

Curative

Curative treatment is on the same lines as in epidemic typhus, except that the elaborate precautions needed in connexion with the louse-borne disease are unnecessary.

(b) *Typhus Fevers of São Paulo and Minas Geraes*

These may have a mortality of more than 70 per cent. The infection is conveyed from rats or other rodents to man by a tick, *Amblyomma cajennense*, and the symptoms of both diseases correspond very closely to those of the more severe types of Rocky Mountain fever. Vector

Animals inoculated with the virus of the São Paulo fever are immune to the virus of Rocky Mountain fever, but the virus of the Minas Geraes fever gives ambiguous results when tested against the São Paulo and Rocky Mountain viruses. Cross immunity

(c) *Fièvre Boutonneuse*

This disease, which is also known as *fièvre exanthématique*, was first described by Conor and Bruch in Tunis in 1910 as 'eruptive fever'. It is now known to be conveyed by a tick, *Rhipicephalus sanguineus*. Dogs are strongly suspected of playing a part in the transmission of the disease as they often give a positive Weil-Felix reaction in places where the disease is endemic. *Boutonneuse* fever occurs in most countries round the Mediterranean (see Plate IX). Vector

The disease resembles the milder forms of Rocky Mountain typhus, the mortality being only 1 or 2 per cent. The points of difference between the two diseases are as follows. (i) There is usually a local necrotic sore at the site of the tick-bite ('*tache noir*') in *boutonneuse* fever; this is uncommon in the Rocky Mountain fever. (ii) The rash of *boutonneuse* fever is more definitely nodular. (iii) Guinea-pigs and rats are not so susceptible to the virus of *boutonneuse* fever and seldom show the scrotal reaction. (iv) The chief distinction is that the virus of *boutonneuse* fever does not protect animals against the virus of Rocky Mountain fever, but on the other hand the virus of the Rocky Mountain fever seems to give some degree of protection against that of *boutonneuse* fever. Evidently *boutonneuse* fever is not identical with Rocky Mountain fever, but further research is needed to decide the exact relation between the two diseases. Diagnosis from Rocky Mountain typhus
Cross immunity

(d) *Tick-Bite Fever of Kenya and South Africa*

These fevers resemble *boutonneuse* fever in most respects. There is usually a sore at the site of the tick bite; in experimental animals there is cross immunity between the South African virus and the *boutonneuse* virus.

(e) *Indian Tick-Typhus*

This form of tick-typhus is of interest as it was the first of the non-epidemic typhus-like fevers to be definitely classed as a member of the typhus group of fevers and also as being the first fever of that group, outside the Rocky Mountain area, in which there was clear evidence that a tick was the vector.

In 1917 J. W. D. Megaw described a case of fever following a bite by a tick in the Himalayan foot-hills which resembled Brill's disease and the milder forms of Rocky Mountain fever; the vector tick was not available History

for identification, but he considered that it was probably either *Rhipicephalus sanguineus* or *Hyalomma aegypticum*. In 1921 he showed that a fever resembling the Rocky Mountain disease, and communicated from wild animals to man by ticks, was common in India and other parts of the world besides the Rocky Mountains. He proposed that this disease as well as the other 'typhus-like fevers' should be regarded as members of the typhus group of fevers and should be classified, provisionally, as 'tick-typhus' and 'mite-typhus' and the classical typhus should be called 'louse-typhus'. In 1934 he emphasized the sharp distinction between louse-borne typhus and the others by dividing the typhus fevers into two main classes, 'epidemic typhus' and 'the non-epidemic typhus fevers', the latter class comprising 'tick-typhus', 'mite-typhus' and 'flea-typhus'. The evidence of the existence of tick-typhus in India, though chiefly clinical and epidemiological, is convincing. It consists in the frequent occurrence of cases clinically indistinguishable from the Rocky Mountain fever in which ticks have often been found *in situ* at the onset of the fever. Although in most cases ticks have not been detected, these cases occurred in circumstances which made it highly probable that a tick had been the vector. Probably many of the cases which have been reported from India as tick-typhus before the discovery of flea-borne typhus were cases of the latter disease or of mite-borne typhus.

*Agglutination
reactions of
Indian typhus
fevers*

Boyd in 1935, dealing with 92 cases of sporadic typhus-like fevers occurring in soldiers in India in which complete agglutination tests were made, found that the serum response in 35 cases suggested mite-borne typhus, in 27 flea-typhus, and in 30 tick-typhus, though no direct evidence of the vector was obtained. In the cases which suggested tick-typhus the response was either strongly positive to *Proteus* OX 2 and slightly positive to OX 19 and OX K, or moderately positive to OX 19 and slightly so to OX K and OX 2.

*Relation to
other typhus
fevers*

The only respect in which Indian tick-typhus differs significantly from the Rocky Mountain fever is the absence of obvious symptoms or scrotal reaction in the few guinea-pigs which have been inoculated. In this respect the Indian disease resembles *boutonneuse* fever, but in view of the absence of scrotal reaction in some exceptionally mild cases of Rocky Mountain fever this point cannot be regarded as conclusive evidence of a specific difference between the diseases.

Mortality

The average mortality of Indian tick-typhus is about 5 per cent, but fulminating cases sometimes occur in localities where the disease is normally mild.

Diagnosis

The differential diagnosis of Indian tick-typhus can usually be established by a history of exposure to the risk of tick-bite or of actual tick-bite: the type of rash, which is usually generalized and rather conspicuous; and the Weil-Felix response, which usually indicates a group reaction rather than a specific reaction, though a high titre response to OX 19 cannot be regarded as excluding tick-typhus in view of the frequency with which this occurs in Rocky Mountain fever. Detailed experimental study of tick-typhus and the other non-epidemic forms of

typhus in India is much needed; the available evidence points strongly to the existence of all three types.

(f) *Differential Diagnosis of Tick-Typhus Fevers*

It is not yet possible to lay down clear rules by which the practitioner will be able in all cases to decide that a case of fever is tick-borne rather than flea-borne or mite-borne. Usually the clinical, serological, and epidemiological features taken together will leave little doubt about the nature of the disease, but in areas where two or even three forms of non-epidemic typhus co-exist difficulties may arise. Mite-typhus seldom gives rise to difficulty; there are very few localities in which it co-exists with tick-typhus and as a rule the consistently high-titre response to OX K in all the local cases can be regarded as strong evidence that a mite is the vector.

*Diagnosis
from
mite-typhus*

Flea-typhus is likely to cause difficulties, as it often co-exists with tick-typhus; but as the latter disease is eminently associated with conditions of the open country, has a more conspicuous and generalized rash, and usually gives a group serum-reaction as opposed to the highly specific response to OX 19 which is seen in flea-typhus, there will usually be little room for doubt. Failure to find positive evidence of a bite by a tick does not exclude tick-typhus; often the tick detaches itself after feeding without leaving any trace of its bite. As a rule the conditions in which the patient has been living give a clue to the likelihood of tick-bite.

*From
flea-typhus*

Association with dogs, especially the removal of ticks from their bodies, is a point of importance, as some persons are believed to have become infected by the entrance of the virus through the skin or conjunctiva rather than by the actual bite of the tick.

*Association
with dogs*

(3)—Mite-Typhus

(*Synonyms*.—Japanese river fever; Tsutsugamushi; pseudo-typhoid of Deli; pseudo-typhus; Mossman fever; Queensland coastal fever; rural tropical typhus; scrub tropical typhus; Sumatra mite fever; endemic glandular fever)

Mite-borne typhus fever is a well defined class of non-epidemic typhus fever though great variations occur in the severity of the disease and even in some of the symptoms. The classical form of the disease is the Japanese river fever which bears the same relation to mite-borne typhus fevers as does Rocky Mountain fever to the tick-borne.

(a) *Japanese River Fever*

(*Synonym*.—Tsutsugamushi)

This is a non-epidemic or epizootic typhus fever caused by *Rickettsia tsutsugamushi*. The virus is conveyed to man from rats or mice by the bite of the larva of a mite, *Trombicula akamushi*. In 1918 Kitashima and Miyajima showed that it was conveyed by the 'red mite'. Between 1922 and 1924 rickettsia or rickettsia-like bodies were described by Hayashi and Takeuchi, Ishiwara and Ogata, Sellards, and Nagayo.

Definition

Geographical distribution The disease has been known for centuries in Japan though its close relation to historical typhus was only recently recognized. It chiefly occurs along the banks of certain rivers on the main island of Japan but it is also found in Formosa, Sumatra, the Malay Peninsula, and China. Probably it also occurs in Queensland, India, Burma, and other oriental countries. The disease has not been recorded outside tropical and subtropical areas in the Orient and has a much more restricted distribution than the other forms of typhus (see Plate IX).

Aetiology The disease is primarily an epizootic of rats, mice, and possibly of other rodents. The causal *Rickettsia*, *R. tsutsugamushi* or *R. orientalis*, is conveyed from infected rats and mice by a larval mite, *Trombicula akamushi*. The accepted view is that the adult mites become infected by biting infected rats or mice and that the infected mites transmit the virus to their offspring which in the larval stage bite human beings and so convey the infection. The larval mites which are very small, only about $\frac{1}{100}$ inch in length, remain attached for several days and convey the virus by their bites.

Virus *R. tsutsugamushi* is very similar in appearance and cultural characters to the other *Rickettsiae* of the typhus fevers. It is pathogenic to monkeys, but the results of inoculations into guinea-pigs and rats vary widely and cannot be relied on for the identification of the disease. In one respect the virus behaves consistently: infected human beings and animals almost uniformly give positive agglutination with *Proteus* OXK and negative with OX 2 and OX 19.

Clinical picture In the Japanese forms of the disease there is almost always a small necrotic sore which appears 3 or 4 days after the attachment of the mite to the skin, accompanied by lymphangitis and lymphadenitis of the associated lymph drainage area. The onset of the fever occurs from 5 to 14 days after the bite. The course of the fever and general symptoms are very similar to those of Rocky Mountain fever, but the common occurrence of the local sore, the infrequent extension of the rash to the palms and soles, and the greater frequency of leucopenia are distinguishing features.

(b) *Varieties of Mite-Typhus*

Pseudo-typhoid of Deli Pseudo-typhoid fever of Deli in Sumatra, which was first described by Schuffner and Wachsmuth in 1909, is now known to be a form of mite-borne typhus conveyed by *Trombicula deliensis* from infected rats. The virus is very lethal to guinea-pigs and rats. The mortality is about 5 per cent in the indigenous population but as high as 40 per cent in Europeans.

Scrub typhus Scrub or rural form of tropical typhus, described by W. Fletcher in the Federated Malay States, has been found to be mite-typhus conveyed by *T. deliensis*. It was formerly supposed that there were two types of mite-borne typhus in the Federated Malay States, one, in which there was a local sore and lymphangitis, being tsutsugamushi, and the other, in which there were no local lesions, being regarded as a distinct

disease. Lewthwaite and Savor showed that the virus of both types is essentially similar, animals inoculated with the virus of one being completely immune to the virus of the other. The presence or absence of the local lesion therefore does not indicate specific differences in the virus. Mossman fever or coastal fever of Queensland is a mild form of mite-typhus conveyed from infected rats by a mite, *Laelaps australiensis*. There is no local sore, but lymphangitis and lymphadenitis are common. Workers in sugar-cane fields which are infested with rats and rat-mites are specially affected.

Mossman fever

The mite-fever of India is a problematic disease, the presence of which in various parts of India is assumed from the occurrence of cases of non-epidemic typhus with a positive reaction to *Proteus OX K* and a negative reaction to the other *Proteus* organisms.

Mite-fever of India

(c) *Diagnosis, Prognosis, and Treatment of the Mite-Typhus Fevers*

Diagnosis is easy in localities where the disease is known to be endemic especially if the local lesions occur, but in places where flea-typhus co-exists cases without local lesions may be difficult to recognize. A strongly positive reaction to *Proteus OX K* is greatly in favour of mite-typhus.

Diagnosis

There are great variations in the mortality. In the Japanese river fever the death-rate ranges from 25 to 60 per cent. In Malaya it is from 10 to 14 per cent; in Sumatra it is 5 per cent in natives and 40 per cent in Europeans; in Queensland it is only 1 per cent.

Prognosis

There is no specific treatment, but convalescent serum would be expected to be effective.

Treatment

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DUODENAL: *See* PEPTIC ULCER, Vol. IX, p. 505

GASTRIC: *See* PEPTIC ULCER, Vol. IX, p. 505; *and* STOMACH, TUMOURS AND SOME OTHER CONDITIONS, Vol. XI, p. 477

PEPTIC: *See* PEPTIC ULCER, Vol. IX, p. 505

RODENT: *See* SKIN DISEASES: TUMOURS, Vol. XI, p. 239

TROPHIC: *See* NEURITIS, Vol. IX, p. 193; *and* NEUROSYPHILIS, Vol. IX, p. 240

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ULCUS MOLLE

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ULTRA-VIOLET RAY THERAPY

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UMBILICUS DISEASES

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UROGENITAL ORGANS,
ABNORMALITIES

1.—EMBRYOLOGY AND ANATOMY

1561.] The umbilicus, owing to the complex structures entering into its formation, may be the seat of most varied lesions, a complete under-

standing of which can be attained only by study of the embryology and anatomy of this and related structures.

The early development of the embryo, its membranes, the yolk-sac, *Embryology* and body stalk is described in the article PLACENTA, DEVELOPMENT AND DISEASES, Vol. IX, p. 652.

In an embryo measuring 0.7 mm., the amnion covers its dorsal *Amnion* surface, the yolk-sac lies ventrally, and the body stalk connects all *Yolk-sac* foetal structures with the placenta. A portion of the yolk-sac, namely, *Body stalk* the allantois, projects into the body stalk. *Allantois*

At this stage the umbilical cord is represented by its chief constituent, the body stalk. By the time the embryo reaches 2.5 mm. in length the

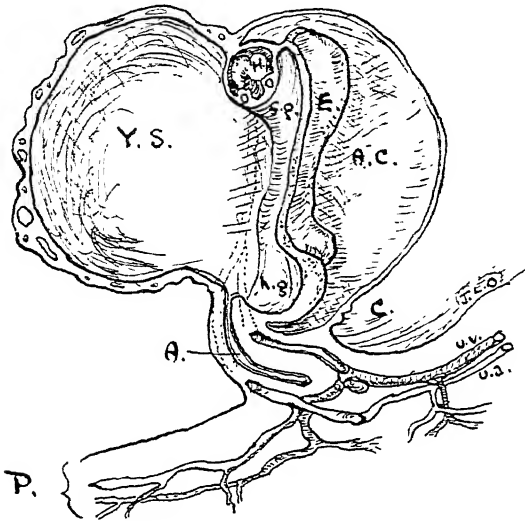


FIG. 24.—Human embryo: sagittal section showing early stage in formation of umbilicus and related structures. A, allantois; C, chorion; E, embryo; H, heart; P, placenta; A.C., amniotic cavity; Y.S., yolk-sac; f.g., fore gut; h.g., hind gut; u.a., umbilical artery; u.v., umbilical vein

primitive cord has appeared and is composed of a narrowed portion of the yolk-sac, called the omphalo-mesenteric or vitelline duct, and the body stalk, both of which pass into the ventral surface of the embryo. The omphalo-mesenteric duct occupies the upper part of the cord and is surrounded by exocoelom; it communicates with the digestive tract. The lower part of the cord contains the right and left umbilical arteries, the umbilical vein, and the allantois. Certain authorities aver that the intra-abdominal portion of the allantois becomes the urachus and is connected with the apex of the urinary bladder. Begg denied this and stated that the urachus is simply the modified superior extremity of the bladder. The urachus at birth reaches to the umbilicus. After birth the bladder descends taking the urachus with it, so that the latter measures 5 cm. in length and its upper extremity is fully 10 cm. from the umbilicus. The omphalo-mesenteric

Omphalo-mesenteric or vitelline duct

Urachus

duct usually disappears early in foetal life but is occasionally wholly or partially patent at birth.

*Anatomy:
superficial
lymphatics*

*Deep
lymphatics*

*Path of
spread for
metastases of
tumours*

The superficial lymphatics draining the umbilicus pass in four directions. From the upper half of the umbilicus they pass to the axillary lymph glands, and from the lower half to the superficial inguinal glands. Deep umbilical lymphatics drain chiefly upward and downward. Those from the upper umbilical region pass on each side of the falciform ligament of the liver, pierce the diaphragm, and enter the mediastinal glands. The lower ones drain into the deep inguinal glands. There is an additional small lymph channel along the course of the round ligament of the liver, along which metastases from cancers of the stomach and gall-bladder reach the umbilicus. Umbilical metastases in malignant conditions in the pelvis may be supposed to have reached the umbilicus by extension along the lymphatics following the course of the remnants of the obliterated umbilical arteries and urachus, i.e. retrograde, by permeation.

In the interpretation of the clinical features of umbilical disorders due attention should always be paid to sex, age, mode of onset and course of the disease, and the state of other structures, as these factors may greatly affect diagnosis.

2.-INFECTIONS

Omphalitis

1562.] Inflammation of the umbilicus in infancy is well known but occurs less often since strict asepsis and routine care of the cord have been recognized as of the greatest importance. Before the era of asepsis epidemics of virulent omphalitis were common, and the mortality was high. Generally the organism responsible is the streptococcus, usually of the haemolytic variety. The staphylococcus, *Bact. coli*, pneumococcus, *Pseudomonas pyocyaneus*, and tetanus bacillus have also been isolated.

In severe cases the umbilicus shows typical signs of inflammation. The child is fretful, febrile, and loses weight. The symptoms depend upon the organs affected, e.g. brain abscess or pneumonia may occur. There may be cellulitis, gangrene of the abdominal wall, septicaemia, and pyaemia.

Sequelae

From the umbilicus, infection spreads along the umbilical vein to the liver, multiple abscesses of which are speedily followed by death. Nuclear jaundice (an extrapyramidal neurological syndrome), umbilical erysipelas, septic spondylitis, and occasionally peritonitis have been described as sequelae to infection. The commonest sequel to mild umbilical infection is the formation of exuberant granulation-tissue (see Tumours, p. 358), with delayed healing of the umbilical stump.

Prophylaxis

The essential points in prophylaxis are strict asepsis when dividing the cord and the use of dry sterile or antiseptic dressings. When infection spreads beyond the limits of the umbilicus the prognosis is

grave, except perhaps in the case of erysipelas, and therapeutic measures are of little avail.

Exuberant granulation-tissue is best treated by bathing the umbilical stump with sanitas or dettol, and thereafter cauterizing with a silver nitrate stick. A sterile dressing should be applied. *Curative treatment*

Sepsis in and around the umbilicus is seldom seen in adults but generally takes the form of pyo-umbilicus. When it does occur it presents certain important problems as there are usually co-existing morphological defects, umbilical concretions, a tendency to chronicity, and a risk of serious complications. It may be due to fistulae, faecal or urinary, but is almost invariably associated with umbilical concretions and foreign bodies, such as dirt, coal, hair-balls, fibres from clothing, and rarely seeds or maggots. A new growth may also be a causal factor. *Pyo-umbilicus*

For treatment see pp. 356 and 357.

Treatment

Tetanus from umbilical infection is no longer common in civilized countries but is encountered among primitive people (see p. 250). For the symptomatology and treatment see article TETANUS, p. 5. *Tetanus*

Montgomery stated that sixty-three cases of diphtheria of the umbilicus were on record, all in infants before the end of the third week. The infant appears healthy and is non-febrile. A diphtheritic membrane may be present. The prognosis is serious and a fatal termination is the rule unless the diagnosis is made early. A culture taken from the umbilicus is invaluable. Antitoxin should be administered in doubtful cases, and in all proven cases. (For dosage see DIPHTHERIA, Vol. IV, p. 99.) *Diphtheria*

The occurrence of syphilis of the umbilicus in the new-born has been described. The ulcer is not unlike a chancre with a round sharply-limited edge and some induration. The diagnosis is proved by a positive Wassermann reaction, positive dark-ground examination of material from the umbilical lesions for spirochaetes, and the discovery of spirochaetes in sections of tissue. The prognosis is fair. For treatment see SYPHILIS, Vol. XI, pp. 592 and 622. *Syphilis*

Primary tuberculosis of the umbilical region is unknown. Babes reported one case of umbilical tuberculosis in a patient with miliary genital tuberculosis. *Tuberculosis*

3.—DISCHARGES

1563.] These may consist of mucus, blood, pus, contents of the small intestine, faeces, urine, or bile. The aetiological factors are described elsewhere (see above, and pp. 356 and 357).

4.—ULCERS

1564.] Simple septic, primary and secondary malignant, tuberculous, and syphilitic ulcers may be seen. (See above, and pp. 358 and 359.)

5.—FISTULA

<i>Congenital and acquired</i>	1565.] Fistula of the umbilicus may be congenital or acquired. The former is due to persistence of the omphalo-mesenteric duct or to incomplete descent of the bladder, practically never to a patent urachus (Begg). An acquired fistula is due to diseases of abdominal or pelvic organs.
<i>Clinical picture: congenital</i>	If the omphalo-mesenteric duct is patent and small, mucus or gas escapes, but when its lumen is large there is free discharge of faeces. When its inner end is closed, a blind fistula lined with mucous membrane and secreting mucus is found. Polypi are not uncommonly associated with this form of fistula, and instances of prolapse of the bowel through a patent omphalo-mesenteric duct are on record. When the bladder fails to descend, a urinary fistula is likely to arise; the urine may be discharged from the bladder directly, through the urachus, or after ascending pre-peritoneal permeation. In the acquired form any of the internal viscera may discharge its contents through the umbilicus, producing biliary, urinary, intestinal, or gastric fistula. Rarely, round-worms and tapeworms have escaped through the umbilicus or umbilical fistulae.
<i>Acquired</i>	
<i>Diagnosis</i>	The nature of the discharge is easily ascertained from physical and chemical tests. Probing may help, but radiological examination following the injection of barium sulphate or iodized oil invariably establishes the diagnosis.
<i>Treatment of congenital form</i>	The treatment of choice in the congenital form is excision of the umbilicus and the fistulous tract. The stump in the ileum or in the bladder is inverted and buried. The treatment of the acquired form is complicated by the nature of the underlying visceral lesion (e.g. tuberculosis or tumours); and the surgeon must therefore be prepared to deal with each case on its own merits.
<i>Acquired</i>	

6.—CALCULUS, CONCRETION, AND CHOLESTEATOMA

<i>Aetiology</i>	1566.] Umbilical concretions are more common in men than in women and usually occur between the second and sixth decades. The condition arises in a deep or stenosed umbilicus in which desquamated cells, hair, threads, and dust are readily retained to form the nucleus of a concretion. Sooner or later inflammatory changes and sepsis supervene with ultimately the formation of an abscess, recurrent abscesses, or the formation of sinuses.
<i>Clinical features</i>	The signs and symptoms are those of inflammation and suppuration. The umbilical depression is distended with pus and with a concretion or caseous material. Although the usual sequel is pyo-umbilicus (see p. 355), desquamative omphalitis with the accumulation of dehydrated

cornified plugs or cholesteatomatous masses has been described. Horns may be found.

Diagnosis is based on the recognition of the type of umbilicus which predisposes to the formation of concretions, and the absence of faecal, urinary, or other forms of fistula. X-ray examination has been of value; some calculi are radio-opaque, and the injection of iodized oil or other radio-opaque substance shows a 'filling defect'. *Diagnosis*

Excision of the umbilicus during a quiescent phase is the only satisfactory treatment. Dilatation gives temporary relief and permits cleansing and dressing before operation. *Treatment*

7.—FOREIGN BODIES

These are described on page 355.

8.—HAEMORRHAGE

1567.] Normally haemorrhage in the new-born is prevented by contraction, retraction, and thrombosis, but haemorrhage may occur a few hours after birth. The time of greatest danger, however, according to Craig, is when the cord comes away. Predisposing causes are morbid states of the blood or blood-vessels, haemophilia, and infection, including syphilis. Males are more often affected than females. In the presence of hereditary defect or haemophilia the prognosis is extremely grave. Fortunately many infants recover spontaneously even after several haemorrhages. *In infancy*

Pressure, and astringents, such as silver nitrate, tannic acid, or adrenaline hydrochloride solution, applied locally may be of value in slight cases. The insertion of a purse-string suture of catgut or silk has proved satisfactory in other instances. Experience has shown that blood transfusion is reliable and effective, the degree of haemorrhage determining the amount of blood transfused. For haemostasis 15 to 25 c.c. of citrated blood are sufficient, but after severe haemorrhage 150 to 250 c.c. will be required. The transfusion is given through either the median basilic vein or the superior sagittal sinus. If oozing persists a further transfusion should be given twelve to twenty-four hours later. Hunt emphasized the importance of 'typing' both donor and recipient, who must be of the same group. *Treatment*

Several cases are on record of haemorrhage from the umbilicus but, as all these patients recovered after local treatment, the origin of the haemorrhage is conjectural. *After infancy*

9.—HERNIA

For a full description of this condition see Vol. VI, p. 494.

10.—TUMOURS

1568.] Simple and malignant tumours have been met with in this situation. Records of the following types appear in the literature: papilloma, granuloma, angioma, fibroadenoma, dermoid cyst, endometrioma, lipoma, carcinoma, and sarcoma.

(1)—Benign

Papilloma

Papilloma is a soft reddish warty protruding mass which may be sessile or attached to the umbilical depression by a pedicle. It is painless and may grow rapidly, bleed freely, and erroneously be regarded as carcinoma. It usually occurs in the uncleanly. Histologically its appearance is typical. It has been found in adults of both sexes and should not be confused with the polypi or granulomas in the new-born. It is treated by radical excision as it is liable to degenerate and become malignant.

Granuloma

Granuloma is a simple form of tumour found soon after separation of the cord. It is a bright-red fungus-like tumour which bleeds easily, and may attain the size of a pea or bean and become infected; usually sessile, it may be pedunculated; its surface is formed by granulation-tissue and not by mucous membrane as in the case of entero-teratoma. The condition should be treated by excision or cauterization.

Entero-teratoma

Entero-teratoma or 'polyp' is a simple tumour closely resembling a granuloma. It is said to arise from distal remnants of the vitelline duct and to become visible after the cord is shed. It differs from granuloma in that it may persist for years and is covered with intestinal mucosa; otherwise its clinical and morbid features are similar. Astringents have no effect on this tumour, hence it should be excised. Ligation may be effective.

Adenoma and fibroadenoma

Adenoma and fibroadenoma are rare and are not usually diagnosed before excision and subsequent histological examination.

Dermoid cysts

True dermoids are rare. Rock believed that they arise in a piece of attenuated umbilical scar which becomes buried in the deeper tissues of the umbilicus. Masses of sebaceous material and hairs, associated with concretions, have been regarded as 'dermoids'. The cysts are seldom large and may break down and discharge a dirty grey foul-smelling material. The surrounding skin becomes red and discoloured. Excision is the appropriate treatment.

Endometrioma

An endometrioma (*synonyms*—endometriosis, endometrio-myoma, adenomyoma, adenomyosis) is a simple tumour composed of glandular tissue and stroma resembling the uterine mucosa. Such a tumour arising at the umbilicus is comparatively rare: it falls into the category of extra-uterine endometriomas. Records of cases were collected by Boggs. (For a full account see ENDOMETRIOSIS AND ADENOMYOMA, Vol. IV, pp. 561, 566.)

*Incidence**Treatment*

Treatment is surgical. Total extirpation of the tumour with a margin

of healthy tissue is never followed by recurrence. Most umbilical endometriomas can be excised without opening the peritoneal cavity.

(2)—Malignant

Cancer of the umbilicus, whether primary or secondary, is rare *Carcinoma* (Wilcox and Greenblatt). Since structures in which cancer originates, namely, hair follicles and sweat and sebaceous glands, are almost absent, primary occurrence is limited. It may, however, arise in vestigial structures, e.g. the omphalo-mesenteric duct. Hence a few cases of Paget's disease of the skin and adenocarcinoma have been described. Irritation from an umbilical calculus has been known to produce carcinoma.

Carcinomatous lesions may be summarized as follows. Primary: (i) *Classification of carcinoma* squamous epithelioma, and (ii) adenocarcinoma. Secondary: derived from stomach, gall-bladder, intestine, ovaries, uterus, and other abdominal organs.

Carcinoma at the umbilicus should always suggest the possibility of a primary intra-abdominal lesion. Probably inguinal metastases in gastric carcinoma are due to secondary spread from the umbilicus.

Primary lesions should be excised and the abdominal cavity explored. *Treatment* Radium or X-ray therapy may be employed. The extensive lymphatic network centred on the umbilicus makes effective treatment uncertain. Secondary carcinoma is at present untreatable.

Only a few cases of sarcoma of the umbilicus are on record, and these *Sarcoma* many years ago. The tumour may be of the spindle-cell or round-cell type. Melanomas have been described. Such conditions are of little importance clinically.

11.—CULLEN'S SIGN

(*Synonym.*—The sign of Hofstätter and Hellendall)

1569.] This rare sign consists of bluish discoloration of the skin in *Definition* the immediate vicinity of the umbilicus. The phenomenon was noted by Hofstätter, but Cullen was the first to recognize its significance and importance, when he described its occurrence in cases of *Aetiology* ruptured extra-uterine gestation. Fallis reviewed the subject of discoloration in acute pancreatitis. As a rule, however, in this condition the discoloration is yellow and generally called 'Grey Turner's sign'; *'Grey Turner's sign' in acute pancreatitis* furthermore it may appear in the flanks, developing many hours after the onset of the illness. Cullen's sign has been noted by Gerrard in ante-partum rupture of a Caesarean scar, and by Goinard and Curtillet in traumatic haematoma of the retro-pubic space (cave of Retzius).

Yellow discoloration at the umbilicus has been observed in rupture *'Halsted's sign'* of the biliary passages; and cyanosis, widely distributed over the abdomen or even the limbs, may appear in acute haemorrhagic pancreatitis. Such a condition is not infrequently referred to as 'Halsted's sign'.

*Mode of
production*

The mode of production of Cullen's sign has not as yet been satisfactorily explained. Stabler suggested that it might be due to a breach of continuity of the parietal peritoneum at the umbilicus, with leakage of blood or its derivatives into the subcutaneous tissues. Petřivalský suggested a lymphatic basis, as there is a rich anastomosis between the lymphatics of the subcutaneous tissues and those of the peritoneum and subperitoneal tissues, and supported his view by experimental evidence. As the sign is rare, it would appear that an anatomical varia-

Value of sign

tion of the structures of the umbilicus must be present. Clinically the sign should be regarded as an interesting phenomenon which is but rarely present in intraperitoneal haemorrhage but may occasionally be of diagnostic value in such cases. (See also Vol. V, p. 260.)

12.—DEFECTIVE UMBILICAL SCAR

1570.] On very rare occasions an attenuated umbilical scar may rupture, permitting escape of abdominal contents. Such a condition is essentially a surgical emergency and is treated on lines similar to those adopted in rupture of an abdominal wound. Pending operation the protruding viscus may be covered with moist sterile saline dressings and a supporting bandage or binder applied.

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UNDULANT FEVER

(*MELITENSIS* AND *SUIS* TYPES)

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Reference may also be made to the following titles:

ABORTUS FEVER PYREXIA OF OBSCURE ORIGIN

1.—DEFINITION

(*Synonyms*.—Brucellosis; (in part) Malta fever, Mediterranean fever, melitensis fever, abortus fever)

1571.] Undulant fever is an endemic and epidemic disease due to *Brucella* of several species, commonly characterized by splenomegaly, leucopenia, secondary anaemia, and pyrexia often of long duration and tending to recur in febrile waves.

2.—HISTORICAL AND GENERAL CONSIDERATIONS

There is little doubt that undulant fever has existed in the Mediterranean region from early times, but it was not until the middle of the 19th century that the disease was sorted out from the heterogeneous group of undifferentiated continued fevers. In 1860 Marston, a British army surgeon serving in Malta, wrote the first published account of undulant fever in which it is recognized and described as a clinical entity (Marston, 1861). From his experience in Malta, Marston suggested that the malady then called 'gastric fever' in England, defined at the time as differing from both enteric fever and typhus, was a form of the disease which he had described in Malta. In support of this opinion he quoted some suggestive passages from an account of gastric fever by Anderson, then a professor of medicine in Glasgow.

*Isolation
of causal
organisms*

In 1886 Bruce isolated the causal organism now known as *Brucella melitensis*, and the researches of the Mediterranean Fever Commission, appointed in 1904, incriminated the goat as the original source of infection. *Br. abortus* was differentiated by Bang in 1897, and *Br. suis* by Trautman in 1914.

*Geographical
distribution*

Undulant fever, once believed to be restricted to the Mediterranean littoral, is now known to be so widely distributed in tropical, subtropical, and temperate countries that it can be classified as a cosmopolitan disease.

Br. abortus
Br. suis

Of the three varieties which are of importance as affecting man, one, abortus fever, has been dealt with already (see Vol. I, p. 68). *Br. suis* infection is more localized in its distribution than the other varieties and is in general an occupational disease, affecting particularly slaughterers, packers, and other workers who may handle swine or their flesh. The male of these animals is more subject to infection than the female, and so in brucellosis of swine abortion has not the suggestive prominence which distinguishes the allied disease in cattle. Common signs of infection in swine are purulent inflammation of lymphatic glands, arthritis, and orchitis. Cattle may become infected by *Br. suis* and transmit the organism in their milk. In man, *Br. suis* infections have no constant clinical characters to differentiate them from other forms of undulant fever. On the whole the disease is not severe and latent infections are common. Exact diagnosis can be made only by laboratory investigations on the lines described later (see p. 373).

Br. melitensis

For the purposes of this article, the term 'undulant fever' without qualification should be taken to mean infection with *Br. melitensis*, not inappropriately as it was for this variety of the disease that Hughes originally proposed the name undulant fever.

3.—AETIOLOGY

*Infection of
animals*

Brucella melitensis infection occurs as a natural disease of goats and sheep. It is sometimes acute and may cause abortion, but often the

affected animals show no clinical abnormality and the existence of infection is demonstrable only by laboratory investigation, such as the recovery of the organism from milk or urine, agglutination tests with blood serum or milk, and the reaction to intradermal injection of antigen. Cows kept in association with infected goats and sheep may also develop the infection, and although these animals do not suffer appreciably in health they may excrete the organism in the milk.

Undulant fever in man is commonly contracted by consumption of infected milk, or milk products, such as butter, cheese, and ice-cream. The disease may also result from direct contact with infected animals or through working with manure. Other possible means of spread are by dust, soil, and water, in all of which the organism may survive for several weeks. Laboratory experience has proved that *Br. melitensis* can readily enter the system through abrasions of the skin or mucous membrane, so that infected discharges and fomites may communicate the disease in various ways. Infection has followed a prick with a contaminated needle, and it is possible therefore that biting insects on occasion serve as mechanical vectors. In human subjects the organism may be excreted in the urine, faeces, and milk, but not, so far as is known, in the saliva or sweat.

Sources of infection in man

Excretion of organism in man

4.—MORBID ANATOMY AND BACTERIOLOGY

The disease has not any distinctive morbid anatomy, and diagnosis can be established at necropsy only by isolation of the causal organism. The spleen is enlarged and congested, the sinuses are distended with blood and lymphoid cells increased in number. The pulp is soft and friable and may even be diffuent. The average weight of the organ is about 18 oz. but weights up to 60 oz. have been recorded. The liver is enlarged and congested and shows a small-cell infiltration around the lobules. Patches of congestion are present in the intestine particularly in the duodenum, upper part of the jejunum, and large intestine, these inflammatory changes sometimes progressing to superficial ulceration of the mucosa. The mesenteric glands are enlarged and soft in consistency. The kidneys share in the general febrile and toxic changes found in the other abdominal organs. At necropsy *Brucella* is most readily recovered from the spleen, liver, and mesenteric glands.

Morbid anatomy

Spleen

Liver

Intestine

Glands

Kidneys

Isolation of organism

Brucella melitensis (*Micrococcus melitensis*) is a small bacillus, 0.6 μ to 1.2 μ long and 0.5 μ to 0.7 μ broad, with many coccoid forms. It is Gram-negative, non-motile, and does not ferment any sugar. Although *Br. melitensis* can grow slowly in ordinary media, its growth is increased in the presence of glucose, blood, serum, or liver extract, and such additions are advisable for recovery of the organism. Continued cultivation on artificial media tends to alter the antigenic structure of *Brucella* thus producing rough variants, a divergence which at one time caused

The organism

Cultivation

Rough forms

much confusion and led to the description of so-called *para* strains. A rough variant may agglutinate with a normal serum.

Identification of types *Br. melitensis*, *Br. abortus*, and *Br. suis* are closely related to one another but may be differentiated by absorption tests. It is often assumed that a *Brucella* isolated from man belongs to the particular species known to be prevalent locally, and although such an assumption may be correct it is desirable when possible to identify it with certainty.

5.—CLINICAL PICTURE

Incubation period The period of incubation lies usually between six days and three weeks, with an average duration of about fifteen days.

Variability of symptoms The symptoms of undulant fever vary widely in their nature, severity, and duration. At one end of the possible range the disease may occur as an intense toxæmia ending in death within a week; and at the other the symptoms may be so mild that it is difficult to convince the patient that he has contracted a specific infection. Similar extremes are seen in other infective fevers, but in those diseases there is commonly recognizable some main and characteristic symptom-group on which the several departures from the normal course can be centred in an orderly fashion. But in undulant fever no case or series of cases can be sorted out and labelled as typical of the malady. It is, however, convenient and helpful to divide the disease into three main types as determined by certain outstanding clinical features; but such groups at the best are unfixed and ill-defined and, although the central members of each may be fairly constant in type, those towards the periphery overlap and intermingle in a confused medley. Further, the symptoms in an individual case may initially conform to those of one group and later take on a different character.

(1)—Types

Undulatory type

Onset The attack generally begins insidiously so that the patient has difficulty in fixing the exact date of onset. The temperature ascends in step-ladder fashion with morning remissions of 1° F. or more, and having reached its highest level at 102° or 103° F. it remains raised for a few days and then gradually falls by a step-ladder descent. In mild cases the temperature may now remain normal and convalescence begin; more commonly after a few days' interval, during which the temperature may be normal, show an evening elevation, or remain raised but at a lower level than before, the fever returns in the form of another wave, to be succeeded in its turn by an interval of absolute or relative apyrexia. Successive waves of fever and intermissions may continue in this way for weeks or months.

The general symptoms resemble those which may be produced in other diseases of bacterial or protozoal origin. Premonitory symptoms,

such as malaise, loss of appetite, weariness, and dejection, are common, against which the patient struggles and tries to keep afoot. Accompanying the fever there are headache, varying in intensity with the degree of infection, increasing malaise, and great lassitude of both body and mind. The patient is hot but shivery and complains of aching pains particularly in the back and neck. Constipation is the rule. The spleen is tender on pressure but appreciable enlargement is usually a later sign. In some cases the mind is clouded and dull, so that this, combined with a furred tongue, and flushed face when the temperature rises in the evening, may give a picture suggesting typhoid fever. In other cases there are irritability, marked restlessness, and insomnia. When the temperature becomes normal the symptoms abate and the attack may appear to have come to an end, but in most cases the relief is only temporary and a recurrence follows.

Premonitory symptoms

Continuous type

It is convenient to place in this group cases characterized by continuous fever without clean-cut intermissions of absolute or relative apyrexia. The temperature often swings over a range of about 2° F. daily; it drops in the morning, perhaps even to normal, only to rise again later in the day. The chart may be 'hectic' with subnormal readings in the morning and a rise to 103° F. or higher in the evening. Again, the symptoms may be so indefinite that the subject is up and about and unaware that he has a slight rise of temperature, perhaps only 99° F., in the evenings. These ambulatory cases may be a danger to others and to themselves, for they can act as carriers, and at any period grave symptoms may supervene or some serious complication develop.

Temperature

Ambulatory cases

In general symptoms there are no essential differences in the types of the disease mentioned above, but the continuous form tends to be more wearing and exhausting to the patient.

General symptoms

Malignant type

Some writers, following Hughes, recognize another clinical group under the name 'malignant'. The symptoms are those which may occur in any case of undulant fever but differ in being much exaggerated in degree. The onset is sudden and the temperature rises quickly to 104° or 105° F. with intense headache, severe muscular pains, and anorexia. Diarrhoea is common with profuse and offensive stools. After a variable period the patient may pass into a deeply toxic state with a dry brown tongue and delirium deepening into coma. Death may result from heart failure, hyperpyrexia, or broncho-pneumonia. In Hughes's series of 45 fatalities in proved cases of undulant fever there were 6 deaths during the first week, 7 during the second, and 9 during the third; i.e. one half of the total number of deaths occurred within twenty-one days.

Temperature

Toxaemia Cause of death

Mortality

(2)—Symptoms and Complications Common to All Types

It is necessary to supplement the foregoing outline by a more detailed account of the protean symptoms of this disease, classified as they may appear in connexion with various systems and parts of the body.

General aspect

The patient's condition, especially at the beginning of an attack, may suggest early typhoid or paratyphoid fever. More usually he is pale, weary, and listless, and as the attack drags its slow length along he may become so wasted and anaemic as to resemble an advanced case of pulmonary tuberculosis. In contradistinction to this, it is surprising how other patients in spite of long-continued fever remain in excellent condition and show few or no clinical signs except an elevated temperature.

Temperature

The undulatory character of the fever is the most constant of the inconstant signs of this disease. The febrile wave commonly lasts from about ten days to three weeks but may extend to six weeks or even longer (see Fig. 25). After the temperature returns to normal there is an intermission of a few days, sometimes ten or twelve, but I have seen febrile relapses after a month of normal temperature. About three relapses is an average number. The temperature commonly climbs and later descends by a series of gradations, but either the rise or the fall may be abrupt.

Undulatory type

When the undulatory type of fever is maintained the recurring waves often become shorter in duration, more markedly remittent, and show lengthening intermissions; but from a study of one wave it is impossible to foretell what characters the succeeding waves may assume. Further, the temperature may begin with one or more undulations and later become continuous. Similarly, though less often, the reverse sequence occurs. Even when the fever is continued, an examination of the chart, especially if 4-hourly records are kept, may show irregular undulatory curves. The daily fever is typically remittent, falling in the morning to 1° or 2° F. below the evening reading; these remissions, especially in the later stages, may be so marked as to give the saw-backed chart of hectic fevers.

Relation of temperature to severity

Except when the temperature is maintained at a continuous high level, over 103° F., it is impossible in undulant fever to gauge the degree of severity of an attack from a study of the temperature chart. Two patients, one of whom is prostrated, wasted, and anaemic, and the other in good condition, enjoying his meals, and interested in all the events of the day, may have identical records of fever. One of my patients was of necessity nursed at home with only a day nurse in attendance. During her sixth relapse with a high remittent temperature, which in most diseases would have implied inability to stir out of bed, she crept downstairs night after night before detection and busied herself in making up her arrears of private correspondence.

Average duration of fever

When undulant fever was widely endemic in the garrison of Malta the duration of pyrexia averaged from two to three months. Individual

cases may far exceed this average and a number are on record in which fever persisted for two years.

In marked contrast to most febrile diseases, the skin is characteristically moist, and even a high temperature, unless this is maintained without remission, does not give subjective sensations of dryness and burning heat. Sensible perspiration is a prominent feature and, especially when accompanying febrile remissions, may amount to drenching sweats which come on after midnight and during the small hours of the morning. This profuse sweating, especially late in the disease, can be very exhausting to the patient and troublesome to his attendants.

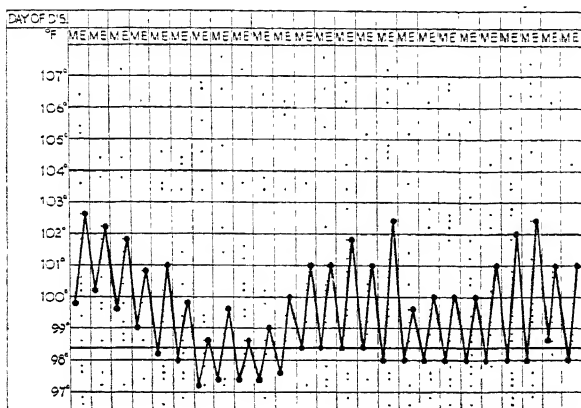


FIG. 25.—Undulant fever (*Br. melitensis*) during tenth month of attack. Patient was cheerful and, except for feeling of heat at night, made no complaint. Good appetite. Spleen ++; Liver +; red blood count 5,200,000; haemoglobin, 70 per cent; leucocyte count 4,000; polymorphonuclear leucocytes, 47 per cent; lymphocytes, 47 per cent. *Br. melitensis* isolated on several occasions from both blood and urine; no blood culture made after sixth month, when organism was still present. Agglutination positive in 1 in 1,000; negative up to 1 in 500. Fever persisted for about two months longer

Other patients pass through an attack even of long duration without perspiring more than is sufficient to keep the skin from feeling hot and dry.

Uncomplicated undulant fever does not produce any characteristic exanthem, but various types of rash may result from excessive perspiration, and prickly heat is sometimes troublesome. One of my patients during a relapse developed an extensive exanthem so like the pleomorphic form sometimes met with in paratyphoid fever as to suggest for a time the possibility of this disease as a concomitant infection.

Staphylococcal boils are a troublesome complication in debilitated subjects, as are small superficial abscesses of the skin due to localized invasion by *Br. melitensis*. As a result of general weakness the hair may fall, which intensifies the prematurely-aged appearance of a wasted subject, but the loss is not permanent.

The tongue is characteristically large, flabby, moist, and furred, with

the tip and edges clean. As a rule the fur is whitish or silvery, and so long as it persists the patient cannot be regarded as free from the danger of relapse however well he may otherwise appear. If a condition of severe debility and anaemia develops the tongue may become in parts red and raw through loss of its superficial epithelium. In the same type of case aphthous ulcers are common in the mouth and the gums become spongy, tender, and bleed readily. In hypertoxic forms of the disease the tongue may take on the dry brown shrunken character found in the 'typhoid' state.

Stomach

Some degree of indigestion is usual and in mild infections may be the only complaint. The patient may describe the symptoms referable to the stomach as a sense of 'fullness' with local tenderness and diminution of appetite; or they may amount to a severe dyspepsia so that many cases of mild undulant fever have run their course under some such symptomatic label. Marked anorexia is not usual in attacks of ordinary severity. Vomiting is rare but may occur at the onset of a severe infection or at the onset of a relapse. On the other hand, even with prolonged fever the appetite often remains good throughout.

*Constipation
and diarrhoea*

As a rule the bowels are constipated or irregular and the stools offensive. Especially in the 'malignant' type, diarrhoea with passage of foul stools may be present early, but at any stage sudden attacks of diarrhoea may be a troublesome complication in a patient previously constipated. Sometimes these can be traced to unsuitable food or to overloading the stomach, but, apart from disturbance due to such dietetic errors, acute symptoms of a dysenteric character may supervene. The stools in such attacks often contain considerable quantities of mucus, and traces of blood, perhaps only microscopic in amount, may be detected, and this without any ascertainable evidence of an added dysenteric infection.

Spleen

The spleen is nearly always enlarged to some extent, as can be demonstrated at first by percussion and later by palpation. The degree of enlargement of the organ is not proportional to the duration of the disease, and in some instances splenic enlargement which originally was easily appreciable on palpation can not be detected later. If the spleen is not palpable, tenderness of the organ may be demonstrated by digital pressure below the costal margin. In addition to splenic tenderness there is a liability to considerable and even very severe pain due to perisplinitis.

Liver

In most cases the liver is enlarged and the lower margin palpable and tender on pressure. Jaundice, usually slight in degree, is occasionally present.

*Respiratory
system*

There is a great liability to involvement of the chest. Even early in the disease catarrh of the air-passages is very common as shown by cough, particularly in the morning. The cough may be dry and ineffective or may give relief by freeing the passages from tenacious mucus.

Cough

Bronchitis

The early respiratory catarrh often progresses to a definite bronchitis, localized or more general. When localized, the base of the lung is most

frequently involved, and a majority of prolonged cases show the physical signs of basal congestion. A much more serious complication is broncho-pneumonia which is a contributory cause of death in most of the cases which end fatally. As in enteric fever, there may be early involvement of the lungs so that the initial symptoms are those of acute pneumonia. Occasionally pleurisy, either dry or with effusion, develops in the course of an attack, a disquieting event as there is always the possibility that a latent tuberculous infection may have become active.

*Broncho-pneumonia**Pleurisy*

The pulse-rate is not affected in any characteristic fashion but varies in keeping with the degree of fever and the general severity of the disease.

Pulse

A secondary anaemia is to be expected. Even when the number of the red corpuscles is fairly well maintained, as it may be whatever the duration of the disease, the haemoglobin is usually considerably reduced in amount. In other cases the anaemia may be so severe as to dominate the clinical picture, giving rise to distressing palpitation on slight exertion or mental excitement, to oedema, and purpuric and other haemorrhages. In the past these symptoms were apt to be aggravated by an added scorbutic element.

Anaemia

The total white-cell count is reduced; in cases of ordinary severity 4,000 to 6,000 cells per c.mm. is an average finding. The reduction affects mainly the polymorphonuclear cells, with a consequent relative lymphocytosis. The large mononuclear cells are normal or reduced in number, actually and relatively. The white-cell response to some septic stimulus may amount to an actual leucocytosis, as in a patient under my care in whom a complicating acute hepatitis of undetermined nature, and not affected by emetine, temporarily raised the white-cell count to 20,000 per c.mm. In similar circumstances when the patient's defensive mechanism has become more exhausted, an increase in the number of white cells, if it occurs at all, is likely to be appreciated only by comparison with counts made before the onset of the septic complication. But a leucocytosis of some degree is possible at any stage and is sometimes found as a late and even terminal event in prolonged infections.

White cells

The heart muscle may show signs of weakness due to toxic degeneration or anaemia. Pericarditis, with or without effusion, and more rarely endocarditis occasionally develop. Ulceration of the cardiac valves, probably a reactivation or extension of pre-existing lesions, has been found after death.

Changes in heart

Among the early symptoms weariness and physical and mental lassitude are outstanding; as the period of toxæmia lengthens, the patient tends to be increasingly depressed. Rarely prostrated enough to be indifferent to his condition, he sees his disease dragging on, or relapse following relapse, and he becomes hopeless and despondent, with outbursts of irritability when he rails at his hard lot. These exacerbations most often follow a fall of temperature. In prolonged and severe attacks there may be some mental confusion and blurring of memory for small details, the latter disability at times persisting far into convalescence. Delirium is not common. The nervous hypertension is characteristically

*Nervous symptoms**Reflexes*

Depression

accompanied by an exaggeration of the deep reflexes. Even in the mild type of case depression, listlessness, and irritability are usual, perhaps being more obvious to the patient's friends than to himself. Thus after two or three weeks of sustained good health which has raised hopes that the disease has burned itself out, the convalescent is obviously losing interest in his pursuits and tires more easily and, although he still protests his good health, his experienced friends realize that another relapse is imminent.

Neuralgia and neuritis

In the late stages, as a result of toxæmia and associated debility, attacks of localized neuralgia and neuritis are common. Any nerve or group of nerves may be affected, including either or both of the sciatics. Areas of the skin, particularly in the lower extremities, become painfully hypersensitive to light touch from involvement of cutaneous nerve-fibres, recalling the 'tender toes' of typhoid fever. The nerve manifestations may progress to a definite peripheral neuritis with wasting, abolished knee-jerks, and foot-drop.

Especially in superficial areas, it is often difficult to say whether a nerve or some associated or adjacent fibrous tissue, e.g. nerve sheath or aponeurosis, is the seat of inflammation. For this reason it is appropriate to point out that fibrous tissue wherever situated is liable to inflammatory involvement. The tendency to neuritis and fibrositis, with the resulting aches, pains, and tenderness, accounts for the high incidence of non-articular 'rheumatism' formerly recorded in the garrison at Malta.

Joints

Arthritis is one of the common complications and in the military cases in Malta was recorded in about 40 per cent. There may be an acute onset with sudden effusion into one of the large joints but more often the involvement is subacute. Except that the acute form sometimes accompanies the initial febrile wave, arthritis is a late complication; but in mild and ambulatory cases its onset may be the first reason to bring the subject under medical notice, or the first to suggest to an alert practitioner the true significance of some preceding indefinite symptoms. The affected joints are painful and tender but are rarely red and do not suppurate. In the subacute form there may be little effusion into the joint cavity, and neighbouring structures and tissues may be affected much more than the articulation. After a few days the inflammation may subside, often only to reappear in some other joints and tending on the whole to move from large to small joints.

Characters of joint lesions

The condition is usually painful and distressing to the patient, and when the intervertebral or sacro-iliac joints become affected every movement may be an agony. In Hughes's extensive series of cases, the joints were involved in the following order of frequency: hip, knee, shoulder, ankle, wrist, fingers, toes, elbow, intervertebral, sacro-iliac, and maxillary. Stiffness, with discomfort on movement, may persist during and even after convalescence, but there is no permanent disability. Tendon sheaths are subject to similar inflammatory involvement and effusion.

Teno-synovitis

Except for the presence of the causal organism, the urinary changes are not diagnostic. The quantity of urine and its constituents are affected by the height of the fever and the amount of sweating. Urobilinogen is increased in amount in a majority of cases. Albuminuria is no part of the disease, though glomerulitis may occur as an occasional complication. In long-continued attacks signs of chronic nephritis sometimes become evident, a development which suggests some pre-existing damage to the kidneys. Severe inflammatory complications of the genito-urinary system, e.g. vesiculitis, may give rise to blood in the urine.

Inflammation of the testis is a recognized late complication and is liable to occur during a relapse. It commonly begins in the epididymis

Changes in the urine

Urobilinogen

Chronic nephritis

Orchitis

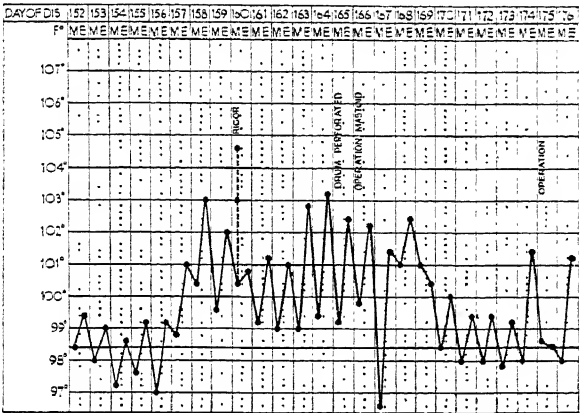


FIG. 26.—Undulant fever (*Br. melitensis*) complicated by acute streptococcal mastoiditis requiring operation on 166th and 175th days of disease, with eventual recovery

and may spread to the body of the organ. Such attacks vary in severity from an acute inflammation with great pain, tenderness, redness, swelling, and effusion, to an affection so mild that a feeling of heaviness in the organ and some tenderness on pressure are the only indications. Usually only one testis is affected, and recovery is complete. Without objective signs of inflammation, patients may complain of neuralgic pain in the testis. In extensive series of cases, the recorded incidence of orchitis varied from 4 to 15 per cent. Ovaritis and also endometritis, sometimes with abortion, may occur.

Ovaritis

The circulating bacteria or their products may affect practically any organ or tissue in the body in such a way as to bring about some complication. In addition to those already noted the following have been recorded: meningitis, encephalitis, myelitis, peritonitis, pyelitis, cystitis, prostatitis, urethritis, vesiculitis, osteitis, otitis media and mastoiditis (see Fig. 26), osteomyelitis, periostitis, mastitis, pancreatitis, parotitis and inflammation of other salivary glands, and phlebitis.

Other complications

6.—PROGNOSIS

In a disease so variable in its course prognosis is notoriously difficult. On the whole an attack with intermissions is more favourable than one with continued fever. A maintained high temperature, a falling agglutination-titre in a patient who remains seriously ill, and persisting asthenia and anaemia are all disquieting signs. The importance of a furred tongue as indicating the danger of further relapse has been already stressed. At any stage the onset of some complication may transform a mild and seemingly favourable case to one of the utmost gravity.

Mortality

The death-rate is low in proportion to the seriousness of the disease as a cause of sickness and invalidism. In the large numbers of cases formerly occurring in the British garrisons in the Mediterranean region the mortality averaged from 2 to 3 per cent. In individual outbreaks, however, the death-rate may reach 10 per cent.

7.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Of the major infective fevers undulant fever is the most likely to be unidentified for often there is little to suggest the diagnosis to one who has not the disease already in mind. The initial detection of an indigenous case in some locality usually leads to recognition of a series of other cases of the disease.

The possibility of a *Brucella* infection should always be entertained in any case of fever of undetermined origin, especially if prolonged, which is associated with leucopenia or at any rate with the absence of leucocytosis. If the pyrexia is of an undulating type, a character found in some 60 per cent of cases, or if there are few objective signs to account for the fever, the probability of undulant fever is increased. Other signs to be looked for are: dyspepsia, a white-coated tongue, the association of fever and a moist skin, an enlarged soft spleen, mental and physical lassitude, arthritis, and orchitis, though these are not necessarily present.

Common symptoms of onset

In ambulatory cases suspicion may be aroused by a history of persistent or recurrent dyspepsia, and formerly medical officers in Malta were advised to take temperature readings in all cases of 'indigestion'. Another common history is that the subject feels well in the morning, but towards the evening he 'crumples up', looks tired and worn, and may be aware of sensations, possibly very slight, of a rise of temperature. The first suggestive event may be the onset of some complication.

Two illustrative personal cases may be mentioned. One man sought advice because of recurring crops of boils of recent origin; and the other, while on holiday in England, developed multiple arthritis which was dogmatically ascribed to dental infection. Although neither would admit to any preceding

definite illness, each gave a history of having felt vaguely 'out-of-sorts' intermittently, over a period of several months. The possibility of undulant fever was strengthened by the fact that both men had come from localities where the disease was known, and consequent laboratory examinations proved this to be present.

In no infective disease is laboratory investigation more important, *Laboratory diagnosis* for without such aid many cases of undulant fever will pass unrecognized and in others the diagnosis will be little better than a guess. As already indicated, undulant fever is more likely to be diagnosed as other diseases than these as undulant fever, and one point that should always bring a *Brucella* infection to mind is a normal or diminished white-cell count in an unidentified fever of more than seven days' *Leucopenia* duration.

In most cases *Br. melitensis* can be recovered from the blood. This is *Blood culture* best taken at the beginning of a febrile wave or, failing this, at the height of the daily excursion of temperature. Flasks of glucose broth or other suitable medium are inoculated and should not be discarded as negative within a period of at least one month. Blood culture is preferably carried out as early as possible in an attack, but the organism may be recovered after months of fever. When it is impossible to exclude infection with *Br. abortus*, a part of the blood withdrawn should be incubated with the special precautions necessary to grow that organism. (See ABORTUS FEVER, Vol. I, p. 73.) *Br. melitensis* is generally present *Urine culture* in the urine at some time, especially during defervescence, though repeated cultures may be required for its detection. In the interpretation of results of the agglutination test, the following suggestions of Topley *Agglutination test* and Wilson relative to *Brucella* infections in general should be considered.

'(1) A titre of 1/80 or less, in the absence of clinical symptoms, is indicative either of a latent *Brucella* infection, or of a past infection—not necessarily attended by definite disease. (2) A titre of 1/80 or over, in the absence of clinical symptoms or of a recent pyrexial attack, is suggestive of frequent infections, usually occurring in persons drinking large quantities of infected raw milk or exposed to contact with infected animals or carcasses. (3) A titre of 1/80 or over in the presence of pyrexia and other symptoms of disease, occurring in a person whose occupation or habits do not expose him to special risk, is very suggestive of active infection with a member of the *Brucella* group. In persons belonging to the occupational classes referred to, in whom a latent infection is not uncommon, a titre of 1/80 is too low to be of diagnostic significance. On the other hand, a titre of 1/1000 or over is rarely met with except as the result of an active infection, and may usually be regarded as evidence of undulant fever. (4) A titre of 1/20–1/80, in the presence of clinically undulant fever, may likewise be considered as practically diagnostic of this disease. (5) The complete absence of agglutinins from a patient's serum does not exclude the diagnosis of *Brucella* infection. Cases are on record in which a positive blood culture has been obtained

in the presence of a negative agglutination reaction. Agglutinins are generally present in a suggestive titre by the end of the 2nd week, and in frank cases of undulant fever they generally rise to a titre of 1/640 or over. After the attack is over they tend to fall fairly rapidly, and may sink to a low level within 3 months. There is evidence that in chronic cases they may fall even during the period of active infection, so that too much stress must not be laid on a negative agglutination reaction in patients whose pyrexia has lasted for some months.

'Attention must be called to the not infrequent occurrence of a prozone, sometimes extending to even 1/640 in high-titre sera. For this reason a wide range of dilutions should always be put up.'

Melitin test

The melitin test is an allergic reaction provoked by intradermal injection of either a filtrate of a broth culture, or a killed suspension, of *Br. melitensis*. In the first-mentioned method, 0.05 to 0.1 c.c. of a 20-day culture may be employed, and in the latter 0.2 c.c. of a killed broth culture containing a million organisms. In a positive reaction a red oedematous area results at the site of injection and persists for two or more days. Control injections in the same subject are necessary. Other forms of antigen, e.g. the saline-soluble portion of bacteria dried *in vacuo* for forty-eight hours, have been devised and employed. The reaction may remain positive long after recovery from an attack of the disease. In its general utility this test is inferior to agglutination.

Diagnosis from enteric group

Undulant fever is commonly confused with diseases of the enteric group, especially during the first weeks. The resemblance is heightened

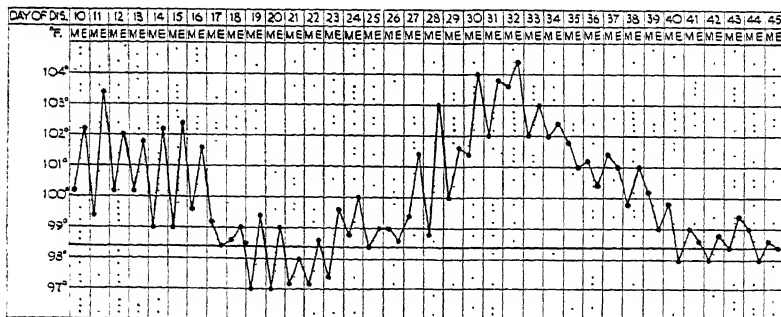


FIG. 27.—Relapse in paratyphoid fever giving temperature curve suggesting undulant fever

by the fact that in the tropics the typhoid rash is often absent and constipation is common. In enteric fever there is as a rule greater prostration in proportion to the temperature, and sweating is not prominent. In mild attacks of typhoid fever, and more commonly in paratyphoid fever, there may be little general disturbance in spite of a high temperature, so that clinical diagnosis is very difficult. The occurrence of a relapse may produce a temperature chart closely resembling that of undulant fever (see Fig. 27).

From amoebic abscess of liver

In undulant fever and amoebic abscess of the liver wasting, anaemia, a prolonged swinging temperature, chills, and drenching sweats may be

present. In liver abscess a leucocytosis of about 15,000 per c.mm. is to be expected. Subjective or objective signs of liver involvement, if these are in evidence, will suggest local examination by screening and skiagrams, and emetine may have a markedly beneficial effect. Amoebic abscess does not of itself cause enlargement of the spleen.

Wasting, anaemia, cough, sweating, and a swinging temperature are common to pulmonary tuberculosis and undulant fever, and differentiation may present a very real difficulty. The occurrence of patches of pulmonary congestion, broncho-pneumonia, or pleurisy in undulant fever may give equivocal appearances in radiographs. Even if demonstrable proof of tuberculosis is forthcoming, concurrent undulant fever is not necessarily excluded. The clinical similarity of these two diseases gave rise to the old belief regarding the hopeful prognosis in pulmonary tuberculosis originating in the Mediterranean region.

The presence of parasites in the blood, and the effect of quinine or other specific drug, should determine the diagnosis of subtertian malaria. Malaria and undulant fever, however, may occur together, and in any patient the demonstration of malaria parasites merely indicates the existence of a malarial infection and does not necessarily imply that all symptoms are due to malaria.

In the first months of kala-azar the sense of well-being, persisting appetite, recurring waves of fever, and the leucopenia have led to confusion. The temperature in undulant fever does not show the double remission of kala-azar, nor is the spleen firm on palpation. The recovery of *Leishmania* from the blood, bone marrow, or liver will settle the diagnosis. A negative aldehyde reaction is strong evidence against kala-azar if the symptoms are of three months' duration. Owing to the greater danger of haemorrhage, splenic puncture should be avoided if *Brucella* infection has not been definitely excluded.

Although there is no sign, symptom, or complication in *Br. melitensis* infection which might not occur in abortus fever, the latter is generally shorter and milder and has fewer complications; and further the causal organism is more difficult to isolate. That is to say, the two diseases differ in the same respects as typhoid and paratyphoid fevers. *Br. suis* infections tend to be milder than those due to *Br. melitensis* but more severe than abortus fever, thus occupying an intermediate position.

Other conditions that may give rise to error or difficulty are: streptococcal septicaemia, especially if accompanied by arthritis; *Bact. coli* septicaemia; ulcerative endocarditis (*Brucella* may be superimposed on valves already damaged); and, in the event of an onset with meningeal symptoms, cerebrospinal meningitis. These infections are associated normally with leucocytosis, an important differential character. Early Hodgkin's disease, when accompanied by febrile waves (Pel-Ebstein type), might suggest undulant fever. On the other hand undulant fever beginning with vomiting and severe diarrhoea, as in the 'malignant' type, has been diagnosed as an infection with one of the food-poisoning

From
pulmonary
tuberculosis

From
subtertian
malaria

From
kala-azar

From abortus
and suis
infections

From other
diseases

group of organisms. The time element will serve to distinguish it from influenza, sand-fly fever, and dengue.

8.—TREATMENT

The enumeration of the possible sources of infection in man (see p. 363) indicates the lines along which preventive measures can be instituted.

There is no specific curative treatment for undulant fever, and the irregular and uncertain course of the disease makes it more than usually difficult to appraise the value of the various medicaments that have been advocated. Temperature charts produced as evidence of the efficacy of some particular treatment can usually be matched by those of other patients treated only on general lines.

*General
reatment*

It is a good practice to preface the dietary regime by a mild purge. No routine diets can be laid down, for the nature and quantity of the food to be given depend on the patient's appetite and power of assimilation. The danger of over-taxing the digestion must be kept in mind. It is well to begin with a basis of milk, sterilized preferably by pasteurization unless the source is above suspicion, and milk preparations—custards, junket if possible, or egg and milk, according to the patient's taste. He should be encouraged to drink daily two or three pints of fresh orangeade or lemonade, with glucose added. The raw yolk of one or more eggs beaten up in orange-juice makes a palatable and nourishing meal. The known essential food factors must be included. Halibut-liver oil, because of its small dose, can usually be assimilated without difficulty. Yeast is an important addition and may help digestion. Fresh brewers' yeast, however disguised, is often distasteful and can be replaced by dried yeast tablets prepared by some reliable firm, giving the equivalent of two drachms of brewers' yeast daily. Marmite in drachm doses is useful as a substitute or variant for yeast. Having proved the patient's capability of absorbing a low diet, the amount of food can be increased, but every untested addition must be made with caution and in small quantity. Here the patient's own inclinations are helpful. Fresh fruit, salads, and the like when obtainable, can be added and, if all goes well, the stage of fish diet may soon be reached. Some patients retain their appetite throughout and do well on a plain ordinary diet, but this should be well balanced and include the accessory food factors mentioned. In such cases it is best to give the main meal in the middle of the day and a light meal at night. If a patient who is taking a fairly liberal diet feels inclined to omit a meal he should not be pressed to eat. Indeed, an occasional day of low diet may stimulate the appetite appreciably.

Yeast

Insomnia

Sleeplessness is both exhausting and depressing and one of the newer synthetic hypnotics, such as sodium barbitone, should be employed without hesitation to secure rest. Excessively high temperatures are

controlled by hydrotherapy; febrifuge drugs are likely to have a depressant effect and are therefore contra-indicated.

Preparations of various metallic salts and dyes have been employed for intravenous injection. They are of doubtful value and none can be regarded as a specific. Sulphanilamide has been advocated in a dosage of $7\frac{1}{2}$ to 15 grains (0.5 to 1.0 gram), thrice daily by mouth, or in an equivalent dosage by injection. In spite of reported successes in some cases there has been no appreciable benefit in others, and a subsequent relapse has not been averted. If no improvement results within a week, the treatment should be discontinued. In debilitated and anaemic patients the drug should be given with caution and its effects carefully watched. Other preparations of the sulphonamide class, known by various proprietary names, have also been used, generally in the dosage recommended by the makers for systemic infections. In spite of some claims to successful results, it is too early to give a final pronouncement on the efficacy of the treatment.

Special treatment

Sulph-anilamide

Vaccine therapy is uncertain in its results but sometimes the treatment appears to be effective. Autogenous vaccines are preferable. Twenty-five to 50 million organisms given intramuscularly is a safe initial dose, and injections in increasing amounts can be repeated at four-day intervals at first, but as a higher dosage is reached the intervals may be lengthened to a week or ten days. Some prefer to give injections of about 10 million organisms on each of several successive days. In the asthenic and non-responsive type of case vaccine therapy should be employed very cautiously and stopped early if no benefit is apparent.

Vaccine

Melitin can be used in treatment as well as for diagnosis. If no general systemic reaction follows the diagnostic intradermal injection of broth-filtrate (see p. 374), larger doses are given intramuscularly. The object is to provoke a febrile reaction, and when the quantity sufficient for this purpose has been ascertained, four fever-producing doses are given at three-day intervals. When the diagnostic intradermal dose causes a general reaction, the same amount is used for the initial intramuscular injection, and the subsequent doses are increased as may be necessary to produce a febrile response.

Melitin

Immune serum if available is worth a trial; as an alternative, 500 c.c. of blood from a convalescent patient, taken with the usual precautions, may be used for transfusion.

Serum

There is some evidence that an attack may be shortened by inducing protein shock. A convenient agent for this purpose is T.A.B. (typhoid-paratyphoid) vaccine, given intravenously in doses of from 50 to 150 million organisms at four-day intervals.

Protein shock

Rainsford devised a method of treatment based on the presence in the urine of urobilinogen in pathological amounts, thus indicating toxic degeneration of the liver cells. A preliminary test is carried out by adding to 5 c.c. of urine three drops of a 3 per cent solution of *p*-dimethyl-amidobenzaldehyde in a mixture of equal volumes of hydrochloric acid and distilled water. The production of a red colour within a few

Rainsford's treatment

minutes shows the presence of urobilinogen in abnormal quantity. In early cases, when the test is positive, he administered glucose 2 to 3 ounces daily in lemonade, and large doses of alkalis, e.g. potassium citrate and sodium bicarbonate by mouth. In view of the liability of intensive alkaline treatment to lower the blood calcium, calcium gluconate 10 c.c. of a 20 per cent solution is given intramuscularly or intravenously once or twice weekly. The treatment usually frees the urine from urobilinogen in from two to three weeks. In chronic or resistant cases, an alternative procedure is to give once daily 10 units of insulin, followed in half an hour by 50 grams of glucose by mouth.

Treatment of complications

Complications must be treated on general lines as they arise. Salicylates are useless and even harmful. Preparations such as allonal (amidopyrine with a barbiturate) ease the aches of arthritis, neuritis, and fibrositis. Morphine should be avoided if possible because of the danger of establishing the habit. If the intolerable pain of some complication makes

Pain

morphine necessary, the drug should be called by some other name in the patient's hearing. Severe anaemia is sometimes benefited in a striking fashion by iron which may be given as freshly prepared Bland's pills. The patient is first tested by giving one pill daily, and it should preferably be chewed before swallowing. If the iron is well tolerated the dose is gradually increased. Even with a continuing pyrexia this treatment may cause a steady rise in the percentage of haemoglobin. In cases of severe asthenia or resistant anaemia, blood transfusion should be undertaken without avoidable delay.

Anaemia

Change of climate

A change of climate, when this is possible, is often effective in hastening recovery or shortening the period of convalescence.

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URAEMIA

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Reference may also be made to the following titles:

COMA NEPHRITIS AND NEPHROSIS

1.-DEFINITIONS AND HISTORY

1572.] The word 'uraemia' should be reserved for certain physical disturbances resulting from severe renal failure. Uraemia implies a clinical state attended by symptoms, together with demonstrable chemical changes in the blood of which the most important is a great increase in the urea content. Severe renal failure, however, may occur and be recovered from without uraemia supervening. In patients with nephritis and hypertension severe symptoms may result from cerebral circulatory disturbance; such cases have often been erroneously labelled 'uraemia' but they should be excluded from the definition and described either as 'pseudo-uraemia' or, following the nomenclature of Fishberg, 'hypertensive encephalopathy'.

In 1833 Richard Bright wrote: 'What seems in some way to account *Historical* for the general derangement and suffering of the constitution is the

fact that urea becomes demonstrable in the circulating mass and the blood becomes impregnated with that substance.' But the word 'uraemia' was first used by Piorry (Piorry and l'Héritier), and at the beginning of the present century the work of Widal and his school in Paris led to the recognition of its true nature.

2.—AETIOLOGY

*Inhibition of
formation and
excretion of
urine*

The aetiology of uraemia is that of severe renal failure; it can be promoted by any process tending to inhibit the formation or excretion of urine. Circulatory deficiency, morbid changes in the kidney including inflammations, tumours, and ischaemic processes, or obstruction to the outflow of urine at any point from the renal pelvis downwards may be responsible for renal failure and uraemia.

When uraemia results from destruction of renal tissue, the destruction must have attained a considerable degree before uraemic symptoms appear. The experiments of Rose Bradford (1892) demonstrated that in animals about three-quarters of the total kidney substance must be removed before uraemia ensues. According to the above definition, uraemia implies a state accompanied by symptoms as well as by chemical change in the blood; when such chemical change is gradual, symptoms will be produced much less readily than when it is abrupt; this explains why a patient with long-standing urinary obstruction from an enlarged prostate will often not show symptoms of uraemia in spite of marked chemical change in the blood, whereas a patient with relatively little renal damage may succumb to uraemia when the renal circulation is impaired as a result of operative shock. (For nephritic oxaemia of late pregnancy see Vol. X, p. 102.)

3.—MORBID ANATOMY AND BIOCHEMISTRY

No morbid anatomical change can be laid down as characteristic in patients dying of uraemia, because the causes of renal failure are so manifold; the morbid anatomy will be that of the processes responsible for the failure of the kidneys in each particular case.

*Nitrogen
retention*

*Blood
calcium and
phosphorus*

Characteristic morbid changes can be found in the chemistry of the blood, the most conspicuous being an increase in the blood urea, but the other nitrogenous substances, particularly uric acid and creatinine, will also be increased. Apart from this nitrogen retention, there is in most uraemic patients a diminution in the blood calcium together with an increase in the phosphorus content. It is easy to demonstrate that this change in calcium and phosphorus occurs almost invariably if blood analysis is carried out in any large series of cases and, for reasons given later (see p. 381), it may be responsible for striking symptoms. The other change in the blood chemistry often present is a

diminution in the alkali reserve; this is important in treatment and is a condition which may carry its own train of symptoms. There is still much to be learned but there has been a singular agreement among trained observers during the last ten years; the recent study by Mason and his co-workers in the United States on the effect of bilateral nephrectomy in dogs amply confirms what is written above.

*Diminution
in alkali
reserve*

4.—RELATION OF CLINICAL TO CHEMICAL PHENOMENA

The clinical phenomena of uraemia include gastro-intestinal symptoms such as vomiting and diarrhoea, drowsiness proceeding to deep coma, nervous manifestations such as increased neuro-muscular irritability and convulsions, and respiratory manifestations such as increased or difficult breathing. All these can be explained on chemical grounds. Care must be taken not to include amongst the clinical manifestations of uraemia phenomena which are really due to other features of renal disease; thus oedema is a result either of albuminuria or of cardiac failure or of both. Pallor may be conspicuous and is in some cases the index of an anaemia which follows renal failure although its mechanism is not yet apparent. Skin eruptions have been described; they are rare but are in some cases uraemic manifestations in so far as their production is related to any excessive secretion of urea in the sweat.

The drowsiness and ultimate coma of uraemia run so closely parallel with the increase in the blood nitrogen that it is difficult to escape the conviction that they are the direct effect of urea intoxication. If it is true that animals can be transfused with urea without developing symptoms, and if it is true that in uraemia certain compounds of phenol of higher anaesthetic potency than urea are found, it is nevertheless unquestionable that the depression of the central nervous system, which forms the major symptom of uraemia, cannot be dissociated from the accumulation of urea in the blood in the manner described by Bright.

Coma

Gastro-intestinal symptoms probably result from the backward passage of urea into the alimentary canal and its subsequent break-down into ammonia.

*Gastro-intestinal
symptoms*

Hypocalcaemia, when marked, is responsible for increase in the tendon-reflexes, twitching of the muscles, and sometimes tetany. Its presence facilitates the occurrence of fits. Diminution of the alkali reserve may produce air hunger or the hissing respiration sometimes so conspicuous.

*Other
symptoms*

If the onset of nitrogen retention, hypocalcaemia, or alkalosis is sufficiently slow these conditions may progress to an extreme degree before any great clinical disturbance is produced.

Relation of uraemia to hypertension

In defining uraemia care must be taken to exclude conditions in which the symptoms are due to cerebral circulatory disturbances rather than to the chemical changes which follow renal failure. Severe hypertension, from any cause, whether accompanied by renal failure or not, may produce a train of cerebral symptoms which can be confused with the manifestations of uraemia. As hypertension is a very common accompaniment of chronic nephritis (see NEPHRITIS AND NEPHROSIS, Vol. IX, p. 144) it is possible for the cerebral symptoms due to circulatory change to be confused with those due purely to the renal disorder. But hypertension accompanies uraemia only in so far as it accompanies those inflammatory and ischaemic conditions which tend to produce severe renal damage.

5.—CLINICAL PICTURE

Onset The onset of uraemia is usually insidious. Even in cases in which a sudden arrest of the renal blood-supply or complete obstruction to both ureters produces anuria, there is usually a latent period of several days before any symptoms are encountered, and in cases in which the renal insufficiency develops much more slowly, such as advancing Bright's disease, prostatic obstruction, or polycystic disease of the kidneys, the onset of symptoms will be even more insidious.

In calculous anuria

Associated symptoms Certain manifestations of chronic renal disease, such as lassitude and anaemia, are not yet understood; when these are present in a patient with renal failure and obvious disturbance of the blood chemistry, it is probably reasonable to classify them as uraemic manifestations and to explain them as originating from chemical intoxication of certain essential tissues of the body. But it is not yet possible to speak with certainty on this point. On the other hand it is logical to describe certain symptoms as definitely uraemic, and these may be conveniently grouped as nervous, gastro-intestinal, and respiratory.

Nervous symptoms

Lassitude Among the nervous symptoms are apathy, constant drowsiness, and a definite interference with mental activity; these are usually the earliest evident effects. The patient falls asleep at work and, although he is easily aroused and often not uncomfortable, his condition resembles that of someone who has not properly emerged from the effects of a hypnotic. Twitchings of the muscles, sometimes fibrillary and sometimes involving large groups, are common symptoms. In such cases the tendon-reflexes are usually exaggerated, but it is doubtful if true uraemia ever produces an extensor plantar response. These muscular manifestations, which at times may produce very painful cramps, are probably results of change in the ionized calcium of the blood. True tetany is rare and is usually seen in cases in which vomiting or some other cause of

alkalosis is prominent. Changes in the retina are absent except in cases which show circulatory disturbance in addition to renal involvement. *Changes in retina*

Gastro-intestinal symptoms

Gastro-intestinal symptoms are present in almost every case. Anorexia, nausea, and vomiting are often the first presenting symptoms. Vomiting usually occurs early in the day and is not related to meals. Diarrhoea is less common but may be very severe and is occasionally accompanied by stools indistinguishable from those of true dysentery. The condition may indeed cause ulceration of the colon, and such ulcers have sometimes perforated. With these manifestations must be considered the unpleasant taste in the mouth which is sometimes the first effect noticed by the patient; a high concentration of urea in the saliva can often be demonstrated in such cases and the same applies to the gastric juice of patients in whom vomiting is prominent. Stomatitis of an ulcerative and even gangrenous character may, in rare cases, dominate the clinical picture, but usually the initial dryness of the mouth proceeds to furring of the tongue and a condition readily explained as being due to a general dehydration and to the gross chemical change in the body secretions. *Vomiting*
Diarrhoea
Unpleasant taste in the mouth
Stomatitis

Respiratory symptoms

Respiratory symptoms are more rare and are usually seen only in the late stages of uraemia. When present they are due almost invariably to acidosis. There is no actual air-hunger but the breathing is of the Kussmaul type; it is quiet and without stertor. Respiratory disturbance, as with the nervous manifestations, is often present in patients with advanced renal disease because of cardiovascular change, but in such cases the symptoms are accompaniments of, and not consequences of, the uraemia. Similarly, it remains very doubtful if there are any true cardiovascular sequelae of uraemia alone; cardiac hypertrophy, cardiac failure, and all their consequences are usually explicable as the results of hypertension. A probable exception is pericarditis which occurs usually as a fibrinous process without much effusion; the diagnosis is usually made either from the discovery of a pericardial rub or at necropsy.

6.—COURSE AND PROGNOSIS

Uraemia is invariably dangerous, but the prognosis in every case depends chiefly on the cause of renal failure. Patients with prostatic obstruction of long standing are often restored to a surprising degree of good health when the cause of obstruction is removed. But when some process such as progressive ischaemic change or polycystic disease is present in the kidney, the onset of uraemia usually heralds death. *Relation of prognosis to cause*

In arriving at a prognosis it is therefore essential to give the most careful consideration to the cause of the renal failure and the course this process is likely to pursue. An abrupt onset tends to indicate renal

failure of recent and acute origin, but an insidious course suggests that time will elapse before the major symptoms become prominent and that renal failure of slow and probably progressive character is present.

7.—DIAGNOSIS

Blood changes

The diagnosis of uraemia must ultimately depend upon the demonstration of chemical change in the blood. History of long standing renal disease or of sudden suppression of urine shortly before the appearance of symptoms may make the diagnosis almost certain but, accepting the present definition of the condition, chemical change in the blood must always be present. This change will always, in uncomplicated cases, be of major degree; unless some important accessory condition, such as circulatory failure, hypertension, or acute infection, is present at the same time as the renal failure, symptoms will not be produced until the blood urea has risen to 200 mgm. per 100 c.c. of blood.

Method of estimating blood urea

The amount of urea in the blood is usually estimated by hydrolysing urea in a protein-free filtrate of the blood to be examined. The urease present in powdered soya bean is employed to produce hydrolysis and a modified form of Nessler's reagent is used in the subsequent distillation process. The amount of urea is calculated after comparison with a standard in a colorimeter. For exact details the reader should refer to standard books on biochemistry. For determining the urea content of blood by the method outlined above only 0.2 c.c. of blood is required, but in the absence of any arrangement with a biochemist it is a safe plan to send 5 c.c. of citrated blood.

Clinical

On clinical grounds alone, e.g. a history of nephritis or other cause of renal failure, a history of recent polyuria, and the presence of albuminuria, together with one or more of the classical manifestations of uraemia, it is often possible to make an accurate diagnosis; but until this has been corroborated by a report on the chemistry of the blood such a diagnosis must be, to some degree, speculative. When the patient is already in coma at the first examination the difficulty of diagnosis may be considerable as coma may result from cerebral vascular change accompanying nephritis. When there is any doubt venesection or lumbar puncture should be carried out as these may be of great help if coma is of hypertensive origin although they are probably useless in true uraemia.

8.—TREATMENT

Removal of cause

Whenever possible, treatment should include measures calculated to remove the cause of the renal failure. Apart from this it must consist in the correction as far as is possible of the abnormal chemical phenomena.

Diet

In view of the nitrogen retention, exogenous sources of urea, such as

protein food, must be reduced to a minimum, and dehydration must be avoided by maintaining a high fluid intake. The diet should include abundant fluids in the form of water and fruit-juice and the calorie value of the diet should be maintained chiefly by readily assimilated carbohydrate such as sugar and starch. A lowered alkali reserve may *Al* be corrected by the administration of sodium bicarbonate either by mouth or parenterally. Hypocalcaemia can be largely corrected by the administration of calcium lactate in large doses or, if the symptoms *Ca* are urgent, by the intravenous or intramuscular injection of calcium gluconate. Constipation, if present, should be treated preferably by *Ap* the use of salts, but in the treatment of this or any other manifestations of uraemia it must always be remembered that elimination is difficult *Diff* and, in consequence, potent substances such as morphine will tend to *elim* produce prolonged effects and must consequently be used with caution. *of*

The uselessness of venesection, apart from its value for the relief of hypertensive phenomena, has already been emphasized. Methods for facilitating the elimination of urea, such as purgation and sweating, must not be lightly condemned. The use of pilocarpine has been virtually abandoned but sweating can in some cases be encouraged with symptomatic and actual benefit to the patient, tepid sponging and gentle radiant baths being the methods of choice.

Total suppression of urine is rare but always extremely grave; it can *Toi* sometimes be overcome by the complete withdrawal of all fluids for *sup* eight hours, followed by the sudden administration of a full pint of *of* water; when this fails intravenous injection of hypertonic saline is sometimes effective, and in extreme cases substances such as cane sugar, which are themselves inert but call for total elimination by the renal system, will sometimes, when given intramuscularly, produce diuresis. The mercurial diuretics are rarely, if ever, of value and decapsulation of the kidneys has not yielded results justifying its adoption.

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URETHRA, DISEASES

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Reference may also be made to the following titles:

ENDOSCOPY OF THE	UROGENITAL ORGANS,
URINARY TRACT	ABNORMALITIES
GONORRHOEA	VULVA AND VAGINA DISEASES

1.—IN MALE

(1)—Anomalies

Congenital atresia of the urethra

1573.] Congenital atresia of the urethra is rare and is incompatible with life unless diagnosed at an early stage. In partial atresia a congenital valve of the posterior urethra occurs as a diaphragm of mucous membrane in the region of the verumontanum and forms a valve, which obstructs the outflow of urine but not the passage of a catheter. The condition is generally diagnosed in the late stages when the urinary tract shows gross evidence of back pressure. Surgical treatment by removal of the obstruction offers a poor outlook; the patient rarely reaches adult life.

Hypospadias and epispadias

These are discussed under the title UROGENITAL ORGANS, ABNORMALITIES, pp. 403 and 405.

(2)—Injuries

Rupture of the urethra is caused by severe blows in the perineum or as a result of fracture of the pelvis. In the absence of injury, spontaneous rupture may result from ulceration of the urethra behind a stricture.

Diagnosis is readily made by the passage of blood from the urethral orifice after a recent trauma: there is also, not uncommonly, an intense desire to pass urine. Evidence of fracture of the pelvis may or may not be obvious. If the tear is in front of the triangular ligament there is usually bruising, varying in degree from a localized area to a large haematoma of the scrotum; but if behind that point, there may not be any local signs.

Treatment should be immediate. The patient should be persuaded to avoid any attempt to pass urine, as this would be followed by extravasation of the urine into the tissues with its sequelae and complications. An attempt should be made to pass a catheter into the bladder. If this is successful, the rupture of the urethra is in all probability only partial and may be satisfactorily treated by an indwelling catheter for a short time; if, however, the attempt is unsuccessful, an extensive or complete rupture of the urethra should be anticipated. In these circumstances an immediate operation should be carried out, consisting of a suprapubic cystotomy combined with an exploration of the site of rupture through the perineum and reconstruction of the torn ends of the urethra over an indwelling catheter. In the presence of extensive bruising of the perineum it may be difficult to locate the proximal end of the torn urethra. Its position can be defined, as a rule, by passing a catheter through the internal opening of the bladder into the perineum. After fracture of the pelvis the prostatic urethra may be completely severed, the prostate being avulsed from the region of the deep layer of the triangular ligament. This damage can as a rule be recognized through the suprapubic wound, after clearing blood-clot collected in the space of Retzius. If it is not possible to suture the damaged ends of the urethra through the wound, the proximal end of the torn prostatic urethra may be approximated to the anterior urethra by an indwelling catheter fixed by a flange over the top of the prostate, holding the ends in apposition by continuous traction on the catheter passing out through the external urinary meatus.

In many cases rupture of the urethra is followed by peri-urethral fibrosis and the formation of a stricture. This can be avoided by immediate operation after the accident, early removal of the indwelling catheter and, in less successful cases, by rigid after-care consisting of regular dilatation of the urethra, even in the absence of obvious stenosis at the time.

Extravasation of urine is a serious complication of pathological or traumatic rupture in which there has been an attempt to micturate. The patients are usually extremely ill, with oedema of the perineum, scrotum, and penis, which eventually extends into the lower abdominal

wall but is prevented by fascial planes from passing into the thighs. In tears of the prostatic urethra this extravasation may not be discovered until the suprapubic region is explored.

Treatment of extravasation In the treatment of extravasation the following principles should be adhered to: (i) a free passage of urine must be secured by suprapubic cystotomy; (ii) free drainage of the fascial planes of the scrotum, perineum, and other areas involved should be provided by multiple large linear incisions; and (iii) repair to the urethra should be postponed until general health permits, unless the passage of a catheter is possible, when it should be left in the urethra.

General treatment Attention to the general health of the patient is the most essential part of the treatment. If the condition of the patient allows, perineal baths may be given in addition to the usual treatment of open incisions. Unless the cause of the extravasation is treated either at the time or at the earliest possible opportunity, a urinary fistula is liable to follow. (See also section on fistula, p. 390.)

(3)—Inflammations

Non-venereal Non-venereal inflammations are caused by organisms other than the gonococcus acquired during coitus. The organisms are varied, and among the more common are staphylococci, diphtheroids, streptococci, and *Bact. coli*.

Treatment Treatment is similar to the local treatment for gonococcal urethritis (see Vol. VI, p. 19). Mercuric oxycyanide solution 1 in 6,000 is a useful irrigating medium in place of the orthodox potassium permanganate. Not uncommonly, however, these cases are unusually resistant to treatment.

Chemical Chemical urethritis is usually caused by (i) prolonged local treatment of the urethra or its too frequent use, or (ii) the use of too strong chemical solutions in the prophylactic or abortive treatment of an early acute gonococcal urethritis. These cases rapidly respond to the cessation of all local treatment and free diuresis.

In the absence of any extrinsic cause for the urethritis, careful search should be made for a local cause, of which foreign bodies and urethral and prostatic calculi are the most common. Rarely urethral discharge may be produced by infection of the bladder or upper urinary tract.

Peri-urethritis and peri-urethral abscess Peri-urethritis and peri-urethral abscess are often associated with acute gonorrhoea or stricture of the urethra. In the early stages the condition may be felt as an oedematous thickening around the urethra, in which fluctuation eventually appears. The abscess is situated either in front of or behind the scrotum, never behind the central point of the perineum, and very rarely to one or other side of the middle line. The position alone is almost sufficient to make the diagnosis.

Treatment Mild cases of peri-urethritis often respond to treatment of the local cause, e.g. stricture, or conservative treatment by hot baths and the local application of heat. If gross suppuration has occurred, drainage is essential; care should be taken to avoid damage to the urethra, which may be running through the centre of the abscess cavity, or a

fistula will result; this may also occur if any predisposing cause, such as stricture, is not treated at the same time.

Spermatorrhoea is a common cause of anxiety in patients. A thick milky discharge occurs during defaecation or straining, or occasionally at the end of micturition. A similar discharge is often noticed after erection of the penis. The history in these cases is usually sufficient to make the diagnosis which may be confirmed, if desired, by microscopic examination of the secretion. The treatment is on general lines, especially reassurance. *Spermatorrhoea*

(4)—Strictures

So-called spasmodic strictures are invariably associated with an acute inflammatory condition of the urethra or accessory organs, such as the prostate, seminal vesicles, and the bulbo-urethral (Cowper's) glands and may result from the attempted passage of instruments. Except as a last resort, instrumentation should be avoided. Attention should be directed to the local condition, e.g. drainage of a prostatic abscess. When this is not feasible, more generalized treatment by hot baths or the administration of sedatives is generally sufficient. *Spasmodic*
Treatment

Traumatic strictures may be diagnosed by a history of injury and their position in the membranous urethra or the bulb; they are rare in the penile urethra. These strictures are generally long and of the so-called tubular type. For this reason, and owing to the large mass of fibrous tissue surrounding the urethra, treatment is often difficult. *Traumatic*

Inflammatory strictures are invariably due to gonococcal infection and are often shorter, of the so-called diaphragm type. Treatment is easier than in the traumatic type. The forms of treatment are described below. *Inflammatory*

Meatal strictures of the external urinary meatus, occasionally associated with primary chancres but more commonly with chancroids, are easily diagnosed but respond less readily to dilatation than do other strictures. A linear meatotomy may be required. *Meatal*

Malignant strictures are generally at the external urinary meatus but occasionally elsewhere in the urethra. *Malignant*

Signs and symptoms

Difficulty in micturition, associated with the passage of a thin stream of urine, is the prominent symptom. There may, however, be extreme narrowing of the urethra associated with retention of urine before the patient comes for treatment. Very dense fibrous strictures may be palpable externally along the line of the urethra, but the diagnosis is only confirmed by the passage of a bougie into the lumen of the urethra to a point of obstruction, or by seeing the stricture through the urethroscope. When passing bougies it is important to start with one of large calibre and work down to the smaller sizes, to avoid damage to the urethra and the possibility of the instrument being held up in a false passage. The hold up of an instrument in a false passage instead of in the lumen of the stricture is readily diagnosed by the fact that it is not

gripped when an attempt is made to withdraw, a sensation usually present with the instrument in the lumen of a stricture.

Treatment

Urethroscopic orientation of the orifice of the stricture in relation to the lumen of the urethra, as well as the position of any false passages, is of the first importance in the careful treatment of stricture. Should there be difficulty in engaging an instrument in the orifice of a stricture owing to false passages, the mouths of any false passages may be deliberately obliterated by passing a bougie or bougies into their lumen, the subsequent bougie passing along the first, unimpeded, into the stricture lumen.

Intermittent dilatation In the more hopeful cases repeated dilatation of the stricture yields good results; frequent dilatations with small increases of calibre, rather than excessive stretching at one sitting, is the method of choice, the latter method tending to produce a tear in the stricture and a resulting increase in the already existing fibrosis; the degree of stretching and length of intervening intervals vary and must be assessed in each case. When a more rapid dilatation of the stricture is desirable, an indwelling bougie should be used, around which the patient passes his urine, the bougie being replaced daily by one of greater calibre. The patient must be in bed.

Urethrotomy In cases in which the stricture is so hard that dilatation by one of the above methods is not possible, or in the resilient type which contracts immediately after dilatation, treatment may be effected by an internal urethrotomy, followed by dilatation.

Excision Excision of a stricture is the ideal form of treatment since, if union by first intention can be secured, after-dilatation is unnecessary. The scope of the operation, however, is limited, as it is only applicable to the short diaphragm type of stricture in the bulbous portion of the urethra. Longer strictures in this region, or even the diaphragm type in the penile urethra, when treated by excision are liable to be followed by a downward chordee during erection.

Impassable strictures Impassable strictures vary in their incidence with the patience and skill of the operator. In such cases, however, treatment must be an open operation or external urethrotomy, followed by subsequent after-dilatation.

(5)—Fistulae

Urethral fistulae are found along the ventral aspect of the urethra and anterior portion of the perineum but may occur in more remote situations. The diagnosis is obvious, but it is essential to differentiate the fistulae with their internal orifice above the vesical sphincter, in which urine leaks continually and not only during micturition, as in the more favourable cases with their internal orifices more distal. The common causes of persistent fistula are: (i) obstruction distal to the internal opening of the fistula, e.g. stricture; (ii) epithelialization of the fistulous track; (iii) rigidity of the walls of the track; and (iv)

communication of fistulous tracks with cavities containing indolent granulation-tissue.

The treatment is on general surgical lines directed towards one of the above causes. *Treatment*

(6)—Calculi

True urethral calculi are generally composed of phosphates and occur in a small sacculus connected with the urethra, making removal through a urethroscope extremely difficult; operation through a perineal approach is generally necessary. *True urethral calculi*

Migrating stones, composed of uric acid, calcium oxalate, or other substances, and coming from a higher level in the urinary tract, may become impacted in the urethra, usually in the fossa navicularis, from which they are readily removed by dilatation of the meatus or, if necessary, meatotomy. They may become impacted in the prostatic urethra, the symptoms being those of acute retention of urine. In this position they may be pushed back into the bladder or be removed through a posterior urethroscope. Open operation may be required. *Migrating calculi*

(7)—Tumours

Papillomas are occasionally seen in the posterior urethra, often associated with a previous attack of posterior urethritis. Similar, although rarer, cases not associated with a previous inflammation but sometimes accompanying bladder papillomas also occur. Haematuria suggests the diagnosis. They are recognized by urethroscopy. Both types are readily treated by diathermy. Massive carcinoma of the urethra is rare. *Papillomas* *Treatment*

(8)—Urethral Shock or Fever

Urethral shock or fever occurs in a small percentage of cases after an instrument has been passed along the urethra. Immediately after the passage of the instrument the patient may show a subnormal temperature, rapid pulse, pallor and vomiting, and rarely death has resulted; at a later stage there are malaise, raised temperature, or even rigors. The condition is best avoided by extreme gentleness of technique, and the patient should go to bed and take plenty of hot drinks as soon after the instrumentation as is conveniently possible. *Treatment*

2.—IN FEMALE

1574.] Morbid conditions of the female urethra are less common than those of the male, stricture, peri-urethral abscess, and such conditions being extremely rare. In view of its position, the female urethra is very rarely injured, except during labour. In these cases, however, the vesical sphincter frequently remains intact, the brunt of the injury falling on the urethra in the region of the triangular ligament; a form of incontinence known as 'stress incontinence' (i.e. during coughing or sneezing) not uncommonly results. This is due to the fact that the vesical *Injury*

sphincter in the female is anatomical in its position rather than physiological in its action.

Prolapse Prolapse of the urethra is rare in males but relatively common in females. It often follows an attack of cystitis but occasionally occurs in young girls, in whom there is no history of previous urinary infection.

Diagnosis Acute urethral pain and dysuria readily draw attention to the condition. On examination, the prolapsed ring of mucous membrane will be seen surrounding the urethral orifice, grossly oedematous and, in the later stages, even gangrenous.

Treatment Replacement is seldom possible, the condition being most readily treated by excision of the cuff of prolapsed mucous membrane with end-to-end suture of the raw edges. The results of this operation are excellent.

Urethrocele Urethrocele is a rare congenital condition, most commonly acquired as a result of injury to the urethra during intra-urethral manipulation or forceps delivery in the female. The prominent symptoms are referred to the urethra as pain during, or dribbling after, the act of micturition, especially if complications such as infection or calculus formation have occurred. The condition is diagnosed as a swelling, often tender, along the ventral aspect of the urethra, from which urine may be expressed. In the acquired type the differential diagnosis from a peri-urethral cavity lined by granulation-tissue may only be possible at operation. Treatment, in those cases causing symptoms, is directed in the first place towards the superadded inflammation, if this has occurred, but an effective cure may be only brought about by excision of the urethrocele.

For caruncle see VULVA AND VAGINA DISEASES, p. 611.

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URETHROSCOPY

See ENDOSCOPY OF THE URINARY TRACT, Vol. V, p. 21

URINE EXAMINATION.

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Reference may also be made to the following titles:

ALBUMINURIA	KIDNEY, SURGICAL
ALKAPTONURIA	DISEASES
CYSTINURIA	NEPHRITIS AND NEPHROSIS
DIABETES INSIPIDUS	OXALURIA
DIABETES MELLITUS	PHOSPHATURIA
GLYCOSURIA	PYELITIS
HAEMATOPORPHYRINURIA	TOXICOLOGY: HOMICIDAL,
HAEMATURIA	SUICIDAL, AND ACCI-
HAEMOGLOBINURIA	DENTAL POISONING
INDICANURIA	URAEMIA
KETOSIS	

1.—COLOUR

(1)—Pigments

Normal colour

1575.] The colour of normal urine may vary from a pale straw to a dark brown but it is usually amber. It depends on the presence of the pigments urochrome and uroerythrin, and as a rule these pigments give their characteristic colour to crystals precipitated from the urine such as urates, uric acid, and phosphates.

Abnormal coloration

In morbid conditions various other pigments, such as urobilin and bilirubin, may be present in the urine, giving it a dark brown to green colour; free haemoglobin gives a reddish-black colour, haematoporphyrin a burgundy-red tint, and red cells a smoky appearance.

Melanogen

In melanomas and very rarely in intestinal obstruction urine may contain a colourless substance known as melanogen. A urine containing this substance is usually normal in colour when voided but assumes a dark brown or black colour when exposed to air by conversion of melanogen to melanin. This reaction may be hastened by the addition of some oxidizing agent, such as bromine water, potassium bichromate, or nitric acid. The development on standing of a black pigment in urine has also been described by Hale White and Janmahomed in their study of urines in cases of pulmonary tuberculosis. The nature of this pigment they were unable to determine.

(2)—Drugs

Urine may be coloured by various drugs, such as aniline dyes, taken by mouth. A yellow colour may be due to rhubarb, senna, or santonin; a blue colour to ingestion of methylene blue; and a brownish-green colour to phenol or its derivatives. A reddish alkaline urine which becomes colourless on addition of acid probably results from the ingestion of phenolphthalein. Sulphonamide compounds have a tendency to cause the urine to assume a reddish colour.

2.—QUANTITY

Fluid intake

The volume output of urine depends on two factors, namely, the amount of fluid supplied to the body and the amount lost through extra-renal channels. The organism receives fluid from three sources: (i) ingested fluid; (ii) ingested solids: the water content of many solid foods is very high, thus tomatoes contain more water than milk weight for weight; and (iii) metabolic water, or that which arises from combustion: the combustion of 100 grams of starch, glucose, and fat gives rise to 55.5 grams, 60 grams, and 110 grams of water respectively. The kidneys normally excrete more than half the fluid eliminated, the remainder being eliminated by expiration, sweat, and faeces.

*Fluid output**Comparison of intake and output*

Normally the total fluid obtained from solid foods and combustion is equal to the fluid lost through extra-renal channels, and this equals about 700 grams. Therefore the volume of fluid ingested as liquid is normally equal to the volume of urine passed, and this averages above

500 c.c. in twenty-four hours. Under normal conditions it is within an error of 5 per cent to consider the fluid ingested as the fluid intake and the total fluid output as the urine output: but in abnormal conditions, such as excessive perspiration, diarrhoea, vomiting, or profuse purulent discharge, this relation does not hold good.

Normally the urine output is 1500 c.c. in twenty-four hours or roughly 1 c.c. per minute. Polyuria is said to be present if the urine passed exceeds 2500 c.c. in twenty-four hours. It occurs in the following diseases: diabetes mellitus, diabetes insipidus, chronic interstitial nephritis, the recovery period of nephritis or heart failure with oedema, and neurosis. Oliguria is present in fever, nephritis of the acute type or with oedema, cardiac failure, diarrhoea, and persistent vomiting.

Increased output

Diminished output

3.—SPECIFIC GRAVITY

The specific gravity of the urine depends on the presence or absence of dissolved constituents. Thus to raise the specific gravity by 0.001 at 15° C. the following quantities of various substances would have to be added to 100 c.c. of urine: urea, 0.36 gram; glucose, 0.27 gram; sodium phosphate, 0.38 gram; disodium phosphate, 0.10 gram; sodium chloride, 0.15 gram; sodium sulphate, 0.14 gram; and albumin, 0.39 gram. So massive an albuminuria as 1 per cent would only raise the specific gravity by 0.003. Normally the specific gravity lies between 1.015 and 1.025 at 15° C. It is necessary to make a temperature correction in the following way: for every 3 degrees above 15° C. add 0.001, and for every 3 degrees below 15° C. subtract 0.001. The specific gravity is very much raised in the highly concentrated urines of fever and acute intestinal obstruction and in diabetes mellitus. In diabetes insipidus and in severe renal impairment the specific gravity is very low.

Diseases altering specific gravity

4.—REACTION

The urine of a healthy person may be acid, neutral, or alkaline throughout the day, depending upon factors such as the nature of the food and the time of its ingestion. The reaction is determined by employing red and blue litmus paper: an acid urine turns blue litmus red, and an alkaline urine the reverse. These changes are clearly seen when the pH of the urine is definitely acid (5.4 or lower) and when it is definitely alkaline (7.8 or higher). Generally the urine of carnivorous animals is acid and that of herbivorous animals alkaline, but either type may alter the acidity of its urine by changing its diet. In a normal healthy individual the urine is acid after fasting, after digestion of protein as a result of production of sulphuric and phosphoric acids, and after the ingestion of ammonium chloride. The urine may become alkaline after any meal to counteract the loss of free acid into the stomach, and after the ingestion of alkalis such as sodium bicarbonate. There is no significant or characteristic change in the reaction of the urine in .

Factors determining reaction

Acid urine

Alkaline urine

*Nature of
deposits*

disease. The deposit which forms in an acid urine is chiefly composed of urates and uric acid: that in an alkaline urine, of phosphates.

5.—ALBUMIN AND BLOOD

Albumin

(See Vol. I, p. 273.)

*Bence Jones
proteose*

In testing for albumin, or more correctly protein, the occurrence of the Bence Jones proteose must be remembered. This proteose is precipitated by heat at 50° to 60° C., whereas albumin precipitates at over 90° C., but the Bence Jones proteose redissolves at the boiling point of water and comes down again in the cold. It is found in 80 per cent of patients with multiple myeloma, and also occasionally in chloroma, tuberculous arthritis, leukaemia, and multiple bone metastases from carcinoma.

Blood, including haematuria and haemoglobinuria

For classification and clinical aspects of haematuria see Vol. VI, p. 97.

Apart from the detection of red blood-cells microscopically, the most satisfactory chemical test for haematuria and haemoglobinuria is carried out in the following way:

*Test for
blood*

To 1 c.c. of urine is added 0.5 c.c. of glacial acetic acid and the mixture boiled and cooled. If blood is present, haematin acetate is formed; 1 c.c. of ether is now added and the mixture inverted several times. The ethereal layer is allowed to separate; this may be assisted by the addition of a few drops of water to the test-tube without shaking. The ethereal layer is pipetted to another test-tube containing a mixture of a few drops of tincture of guaiacum and 1 c.c. of ozonic ether. A blue colour develops in the presence of blood.

This test is specific for blood and excludes such substances as iodides, pus, and other compounds which give a blue colour when added to tincture of guaiacum and ozonic ether.

6.—CASTS

The origin of casts is not known with certainty. They are probably derived from protein in the urine, the coagulation occurring in the tubules as a result of some vascular lesion in their walls. Granular, epithelial, fatty, and lipid casts contain remnants of tubular epithelium in various stages of degeneration. The following types of casts are recognized: (i) hyaline: pale, transparent, and homogeneous; (ii) granular: packed with renal epithelial cells; (iii) epithelial: containing cells from renal tubules and the precursors of the granular casts; (iv) fatty: epithelial casts with fat droplets, found in severe degeneration of the renal epithelium; and (v) waxy: similar in appearance to hyaline casts but longer and broader; these probably arise from hyaline casts by condensation as a result of long stay in the tubules. They are found not only in amyloid disease but also in severe degenerative lesions.

Types

*Amyloid
casts*

Much confusion has arisen over the identification and significance of amyloid casts. In amyloid nephrosis as a rule the tubules contain casts in great numbers, and these casts do not give the staining reactions of

amyloid. Casts have, however, been detected in amyloid nephrosis which do give the amyloid staining reaction, and it is probable that this is explained by the fusion of the basement membrane of the tubule with the epithelial cells, the whole mass then being cast off.

The significance of casts has long given rise to controversy. A few hyaline casts have probably no significance and are often found in benign albuminuria. Granular, epithelial, fatty, and waxy casts, however, all point to chronic degeneration. *Significance of casts*

7.—CHEMICAL CONSTITUENTS

(1)—Oxalates

(See OXALURIA, Vol. IX, p. 343.)

(2)—Chlorides

Chlorides are excreted in the urine chiefly in combination with sodium but also in small amounts with potassium, ammonium, and magnesium. The daily output is about 15 grams of chloride expressed as sodium chloride, so that the concentration in the urine is roughly 0.1 gram per 100 c.c. Chlorides are introduced into the body chiefly in food and as sodium chloride. The output of chlorides is diminished in pneumonia at the crisis and for the two succeeding days; also in febrile conditions, nephritis—particularly when oedema is present, typhus and rheumatic fevers, and in malnutrition when the intake by the mouth is low. Increased output of chlorides during the rapid absorption of exudates from the body has been described. *Normal output*
Diminished output
Increased output

Chlorides can easily be detected by the addition of nitric acid and silver nitrate to the urine. Normally a heavy white precipitate appears, but in conditions associated with a diminished output a mere turbidity is present. *Detection*

(3)—Sulphates

Sulphates are excreted as inorganic sulphates chiefly combined with sodium and potassium and as ethereal sulphates in combination with phenol and indol. The synthesis of these ethereal sulphates has been described in the article INDICANURIA (see Vol. VII, p. 111). The normal daily output of sulphur is about 1 gram. The output is increased in acute toxic hepatitis, in fevers such as smallpox, typhus, and pneumonia, and in diabetes. The output is diminished in nephritis and amyloid disease. *Increased output*
Diminished output

Sulphates may be tested for by adding to the urine first acetic acid to avoid precipitation of phosphate and then a solution of barium chloride. A white precipitate indicates the presence of sulphates. *Detection*

(4)—Urea

Urea represents the ultimate product of protein metabolism. It is formed almost exclusively in the liver but a small amount appears to be formed elsewhere in the body. A normal adult on an ordinary diet

Normal excretion

containing about 80 grams of protein a day excretes about 30 grams of urea in the urine in twenty-four hours. On a normal volume output of 1500 c.c. this would make the concentration of urea in the urine about 2 grams per 100 c.c. Conditions such as a large intake of nitrogenous food, excessive break-down of protein tissues through exercise, acute fevers, and diabetes mellitus promote a loss of urinary urea greater than normal. The output of urea is diminished by a low protein intake, nephritis, and acute necrosis of the liver.

Conditions altering excretion

(5)—Uric Acid

The excretion of uric acid is less than 1 gram daily, or only 5 per cent of the total nitrogen in urine, but in birds and reptiles uric acid is the chief nitrogenous constituent. The uric acid excreted is derived from two sources, exogenous and endogenous, in about equal amounts. After a large intake of uric acid by mouth only a small amount of it is excreted in the urine, and it seems probable that uric acid is destroyed in the body. The output of uric acid is increased in pneumonia, leukaemia, in any condition associated with marked leucocytosis, and in pernicious anaemia. In gout it is believed that for a few days before the attack the excretion of uric acid falls and after the attack the output is increased.

Factors altering excretion

Detection

Uric acid may be precipitated from the urine in the form of so-called 'cayenne pepper' crystals which have a characteristic appearance microscopically. A chemical test known as the murexide test can also be employed in its detection; this consists of adding a drop of nitric acid to the crystals and evaporating to dryness on a water-bath. A reddish spot appears and becomes deeper in colour on addition of solution of ammonia.

Murexide test

(6)—Bile

Test for bile salts

The simplest test for bile salts and by far the easiest for clinical purposes is Hay's test, which consists in sprinkling dry flowers of sulphur on the surface of the fresh cool urine in a glass beaker, employing a normal urine as a control. If bile acids are present the flowers of sulphur sinks through the urine owing to its lowered surface tension.

Tests for bile pigment

Froth test

Several tests for bile pigment have been described. The froth test is a very simple test consisting of shaking urine vigorously and comparing the froth produced with that from a normal urine. In the presence of bile pigment a greenish tint will be imparted to the froth, easily discernible by comparison with the control.

Iodine test

The iodine test consists of carefully adding a few drops of 1 per cent alcoholic solution of iodine to about 1 c.c. of urine in a test-tube. A green ring forms and after shaking the urine becomes green.

Gmelin's test

Gmelin's nitric acid test consists in adding the urine to concentrated nitric acid without shaking in order to produce a junction between the two liquids. At the point of contact of urine and nitric acid a play of colours will appear.

(7)—Ketone Bodies

The ketone bodies found in urine are three in number, namely, acetoacetic acid, β -hydroxybutyric acid, and acetone.

The addition of ferric chloride to a urine containing acetoacetic acid produces a Bordeaux red colour. This colour reaction may be imitated by the urine of subjects who have ingested salicylates or aspirin. The test should therefore be repeated after a sample of urine has been boiled vigorously for five minutes. By this process the volatile acetoacetic acid is driven off and a subsequent test should be negative. *Aceto-acetic acid: ferric chloride test*

A more sensitive test consists in saturating the urine with ammonium sulphate, and the addition of a weak solution of sodium nitroprusside followed by strong solution of ammonia. In the presence of acetoacetic acid a permanganate colour develops. This is known as Rothera's test. *Rothera's test*

Rothera's test, but not the ferric chloride test, is positive in the presence of acetone. *Acetone*

(8)—Alcohol and Sugar

The alcohol is separated from the urine by distillation. A distillate equal to one-fifth of the volume of the urine is collected. Portions of the distillate are tested as follows. (i) For Lieben's iodoform test 5 drops of 10 per cent potassium hydroxide solution are added to a few c.c. of solution and the mixture is heated in warm water for 5 minutes; 5 per cent iodine dissolved in 10 per cent potassium iodide solution is added drop by drop until a permanent brown colour is obtained. This colour is discharged by the cautious addition of more 10 per cent potassium hydroxide solution. A characteristic smell of iodoform is given by alcohol, aldehyde, or acetone. (ii) Two grams of anhydrous sodium acetate are added to about 2 c.c. of distillate. An equal volume of strong sulphuric acid is added and the mixture warmed. The characteristic fruity odour of ethyl acetate denotes the presence of alcohol. (iii) To another portion of the distillate three volumes of concentrated nitric acid containing 0.5 per cent potassium dichromate is added. A blue-violet colour appearing in a few minutes in the cold is due to alcohol or aldehyde but is not given by acetone. (iv) To 5 c.c. of distillate 1 c.c. of 2 per cent potassium dichromate and 5 c.c. of concentrated sulphuric acid are added and the solution is boiled for one minute. In the presence of a reducing substance a greenish tinge or a pure green colour is produced. *Detection of alcohol in urine*
Lieben's iodoform test

Tests for sugar in the urine are described in the article GLYCOSURIA, *Sugar* Vol. V, p. 593.

8.—TESTS OF RENAL FUNCTION

The biochemical tests of renal function may be classified as (i) examination of the urine; (ii) examination of the blood; (iii) the ability of the

kidneys to concentrate and dilute urine; (iv) the effectiveness of the kidneys in eliminating introduced substances; and (v) simultaneous studies of blood and urine.

Examination of the urine Examination of urine comprises a study of the volume output in twenty-four hours, the specific gravity, the centrifugalized deposit, and the detection of protein and blood. These examinations have already been described in the earlier part of this paper.

Examination of blood Examination of the blood consists of measuring the concentration of various constituents, such as urea, creatinine, uric acid, non-protein nitrogen, the plasma proteins, and alkali reserve.

Concentration and dilution of urine The third group of tests is carried out by finding if, after a twelve hours' fast and twenty-four hours' dry diet, the urine can be concentrated to a specific gravity of 1.030. Normally this should be possible. The dilution test depends upon the ability of normal kidneys to excrete a large volume of water three hours after its ingestion.

Excretion The fourth group depends on excretion by the kidneys of foreign substances, such as methylene blue, fuchsin, indigo carmine, and phenolsulphonaphthalein. Normally, 40 to 60 per cent should be excreted in the first hour and 20 to 25 per cent in the second hour.

Simultaneous studies of blood and urine The simultaneous studies of blood and urine—blood clearance examinations—are probably the most accurate, and recently tests based on this type of investigation have been popularized by van Slyke and his collaborators who have devised a simple formula for renal function provided the volume of urine passed exceeds 2 c.c. per minute. The formula is:

$$\frac{\text{mgm. of urea in urine}}{\text{mgm. of urea in blood}} \times \text{volume in c.c. of urine per minute.}$$

In normal people the figure is about 75 and to express any result in terms of normal (called 100 per cent) it is multiplied by 100/75. These observers found that a renal function of under 40 per cent of normal four months after an acute attack of nephritis indicates a bad prognosis. Uraemia develops if the renal function falls below 10 per cent.

Malingering For alterations made in the urine by malingerers see Vol. VIII, p. 360.

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UROGENITAL ORGANS, ABNORMALITIES

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Reference may also be made to the following titles:

FALLOPIAN TUBES DISEASES	TESTIS AND CORD
FOETUS DISEASES, MAL-	DISEASES
FORMATIONS AND	TESTIS, UNDESCENDED
MONSTROSITIES	URETHRA DISEASES
OVARY DISEASES	UTERUS, DISEASES
PROSTATE DISEASES	AND DISORDERS

1.—KIDNEYS, URETERS, AND BLADDER

(1)—Ectopia Vesicae

(*Synonym.*—Exstrophy of the bladder)

See BLADDER DISEASES, Vol. II, p. 398.

(2)—Diverticulum

See BLADDER DISEASES, Vol. II, p. 400.

(3)—Persistent Patent Urachus and Cysts of the Urachus

Embryology 1576.] The bladder is developed from a portion of the primitive yolk sac, the cloaca. The allantois, a tube-like outgrowth from the same sac, extends from the cloaca out into the primitive umbilical stalk. Normally this outgrowth undergoes retrogressive changes and, at birth, is represented by a band of connective tissue leading from the apex of the bladder to the umbilicus. This band is called the urachus. By failure of obliteration of the lumen of the allantois, the urachus may remain patent in whole or in part.

Patent urachus

Complete patency If after birth the lumen of the urachus is complete from the bladder to the umbilical cord, urine will escape from the umbilicus. There may be only a few drops at each micturition or almost the whole of the urine in the bladder may be voided in this way. If the lumen is open at the umbilical end but closed at the bladder end there may be a constant discharge of mucus at the umbilicus and the tract is very liable to become infected. If the lumen is open only at the bladder end there will probably be no symptoms, unless at any time there is obstruction to the outflow of urine from the bladder, in which event a diverticulum from the bladder may develop. If the lumen is shut at both ends but remains patent in any other part a urachal cyst may form.

Urachal cyst

Clinical picture A simple urachal cyst gives rise to a tense swelling, dull to percussion, lying in the middle line between the symphysis pubis and the umbilicus. It may not appear until early adult life and then the patient may notice the swelling or complain of pain in that region. Alternatively the swelling may be found in the course of a routine examination.

Differential diagnosis The cyst may be mistaken for a distended bladder or an ovarian cyst; a catheter should always be passed to exclude the former. These cysts are very liable to become infected, and then may cause confusion in diagnosis. The localized pain, tenderness, and oedema of surrounding tissues will suggest a localized abscess due to other causes, such as appendicitis, diverticulitis, or tuberculous peritonitis. A positive diagnosis will often be made only at operation.

Treatment The treatment of patent urachus and urachal cysts is surgical. In

uncomplicated cases excision of the tract or cyst is safe and gives good results. In the case of infected cysts, however, it may be unwise to attempt primary excision and more cautious measures should be taken by primary drainage and excision at a later date.

2.—URETHRA

1577.] The urethra is developed as an outgrowth from the ventral *Development* portion of the cloaca. Primarily, the anterior urethra is represented by a groove in the under surface of the penis, which is gradually converted into a canal by fusion of its lips; the proximal portion is closed first and the fusion gradually spreads distally. The prostate, Cowper's glands, and Littre's glands develop as outgrowths from the urethra.

(1)—Double Urethra

True duplication of the penis and urethra has been reported in a few cases only. A more common malformation is a second canal leading from the bladder and opening on the exterior of the penis. This accessory canal is nearly always dorsal to the normal urethra and opens on the dorsum of the penis proximal to the glans. In some cases the accessory canal does not reach the bladder but leads from the external opening to end blindly behind the symphysis pubis. Ventrally situated there are occasionally abnormal openings which, when traced *Congenita urethral fistulae* backward, join the normal urethra and for this reason are sometimes called congenital urethral fistulae. A type of short blind duct, usually designated para-urethral duct, opens near the external urinary meatus *Para-urethral ducts* or into the fossa navicularis. These ducts may be single or multiple and are common in hypospadias. They are important because they are liable to harbour infection, e.g. gonorrhoea.

(2)—Hypospadias

(a) Definition

In this condition there has been defective closure of the primitive urethral groove so that the external urinary meatus is on the ventral surface of the penis proximal to its normal position.

(b) Types

The external opening of the urethra may be in any ventral position between the perineum and the glans. The various positions of the opening are usually described as glandular, penile, peno-scrotal, scrotal, and perineal.

The glandular is the commonest type and includes all those cases in *Glandular* which the opening is between the normal position and the coronal sulcus. The fossa navicularis may be formed and the urethral opening be within it, but very narrow and contracted. This condition is

sometimes described as concealed hypospadias. In other cases the glans, which is broadened and flattened from before backwards, has a shallow groove with the opening of the urethra at the bottom of it. The glans is covered on its dorsal surface by the prepuce which is absent on the ventral surface as also is the frenum, and the prepuce is described as a hood over the glans.

- Penile* In the penile type the opening is anywhere on the ventral surface of the penis between the coronal sulcus and the peno-scrotal junction. There is generally a shallow groove leading from the opening to the glans. The same deformities are present as in the glandular type, namely, the flattened glans and the hooded prepuce, but, in addition, a fibrous cord extends from the meatus to the glans and draws these two points together, producing curvature of the penis. This is noticeable in the flaccid condition of the penis but when erection occurs it is most marked, producing the condition known as chordee. The farther the external meatus is from its normal position on the glans the more marked is the chordee.
- Curvature of penis*
- Chordee*
- Peno-scrotal* In the peno-scrotal type the opening is at the junction of penis and scrotum. The same deformities are present and chordee is marked.
- Scrotal* In the scrotal type the scrotum is generally cleft with one testis in each half. The penis is very much drawn down and hidden by the redundant preputial fold.
- Perineal* In the perineal type the genital region resembles that in the female and a mistake may be made in determining the sex of the infant. The scrotum is entirely bifid and, as there may be an associated mal-descent of the testes, the two halves of the scrotum resemble the labia majora. The penis is small and contracted, resembling the hypertrophied clitoris.

(c) *Clinical Picture*

- Only the penile portion of the urethra is affected in hypospadias and the normal control of micturition is not influenced in any way. The abnormal opening of the urethra, however, is very liable to be small, so that symptoms of urinary obstruction may be produced. If a child without any obvious deformity complains of difficulty in micturition or even acute retention, concealed hypospadias must be borne in mind. Other symptoms which may call attention to the deformity are associated with the urinary stream or the act of coitus. The stream is directed downwards and a male child may have to urinate in the squatting position. Owing to the congenital chordee, coitus may be difficult or impossible. Finally, in extreme cases, errors may be made in the determination of sex and a male child brought up as a female (see Vol. V, p. 366).
- Urinary stream*
- Coitus*

(d) *Treatment*

Glandular hypospadias and the lesser degrees of penile hypospadias may cause no disability to the patient and do not call for treatment. The presence, however, of a stricture or, in the more advanced degrees,

of chordee and the mal-direction of the urinary stream will require surgical treatment.

Strictures will yield to simple dilatation but two problems are presented by the advanced cases: (i) the ventral curvature of the penis and (ii) the absence of a greater or lesser part of the penile urethra.

The first thing to be done is an operation with the object of straightening the penis, but it is difficult to decide at what age this preliminary operation should be undertaken. The younger the child, the smaller the parts and the more difficult the operation. On the other hand, as the child grows the deformity becomes more marked and normal development cannot occur. It is probably wise to undertake the first operation as soon as possible, generally in the second or third year. The penis may then be left to develop normally and the second operation done at a later date. The straightening operation is simple and performed through a transverse incision on the ventral surface of the penis just proximal to the glans. All fibrous tissue is excised and the incision sewn up longitudinally. When the operation is completed the urethral opening is very much further from the end of the penis than it was previously.

*Straightening
the penis*

*Primary
operation*

Technique

*Second
operation*

At least six months should elapse before any further operative procedure is undertaken, no matter at what age the preliminary operation has been done. The best age at which to undertake the second operation for reconstruction of the urethra is probably after seven years but before puberty. At this time the parts will be larger, a measure of co-operation will be obtained from the child, and sexual development will not have advanced too far, with frequent erections and seminal emissions.

*Reconstruction
of
urethra*

*Principle of
operation*

Technique

The object of the second operation is to construct a new urethra which will convey the urinary stream from the abnormal opening to the end of the glans penis. The number of different methods which have been employed in carrying it out bears testimony to the difficulties of the procedure. The principle underlying all the operations is to make a tube of skin, with the epithelial surface on the inside, and plant it subcutaneously on the ventral surface of the penis so that it is united to the existing urethra at one end and emerges on the glans penis at the other. The tube of skin is obtained either by local flaps from the redundant prepuce, or as a whole or Thiersch graft from some other part of the body. A completely successful result may be obtained at one operation but strictures and urinary fistulae are very common complications and several secondary operations may be necessary before a good result is obtained. More than in any other branch of surgery, the best results are obtained by those surgeons who are frequently called upon to perform these operations.

(3)—Epispadias

Epispadias is a deformity in which the urethra opens on the dorsal surface of the penis proximal to its normal position. The condition is also found in the female, the urethral orifice being above the clitoris. It

Definition

is much rarer than hypospadias and bears a close relation to ectopia vesicae.

<i>Types</i>	There are two main types of the condition, penile or clitoric, and complete. The essential difference between the two is that control of micturition is present in the first but absent in the complete form. In the penile or clitoric type the urethral orifice is on the dorsum of the penis or clitoris, generally near the base. The prepuce is absent on the dorsum and the penis atrophic. A groove extends along the dorsum of the penis from the meatus to the glans. In the complete form the urethra appears to be entirely absent and the bladder opens directly to the surface in the region of the symphysis pubis. The pubic bones, as in ectopia, are generally not united. Interference with sphincteric control of the bladder, due to the malformation, results in incontinence.
<i>Penile or clitoric</i>	
<i>Complete</i>	
<i>Symptoms</i>	In most cases the diagnosis is obvious but in the more severe degrees, especially in females, it may be overlooked. Incontinence may then be the only symptom calling attention to the deformity. Disturbances in sexual function are often associated with epispadias. The small size of the penis and the position of the orifice may make coitus impossible.
<i>Treatment</i>	In the penile form, without incontinence, a plastic operation on lines similar to those described for hypospadias will produce good results. Complete epispadias presents a different problem because the internal and external sphincter muscles of the bladder have both failed to unite anteriorly.
<i>Young's operation</i>	Young described, and claims good results for, a radical operation for the cure of this condition, consisting in excision of the fibrous tissue replacing the muscle fibres of the sphincters, and resuture. This is combined with a plastic operation.

(4)—Congenital Obstruction

<i>Causes</i>	Congenital obstruction may be due to urethral occlusion or urethral valves. Complete atresia of the urethra may appear in the male or female foetus, or there may be an epithelial occlusion at the meatus or in the length of the urethra. There will be complete urinary retention in the foetus with consequent hydronephrosis and hydro-ureter. Congenital valves occur in the posterior urethra and give rise to chronic urinary obstruction. The condition is by no means uncommon and now that the symptomatology is becoming recognized more cases are diagnosed.
<i>Urethral occlusion</i>	
<i>Urethral valves</i>	
<i>Types of valve</i>	These valves are all situated in the neighbourhood of the verumontanum. The commonest form consists of two flap-like folds extending distally from the lower border of the verumontanum on the floor of the urethra, arranged rather like the valves in the venous system so that they flap forward and obstruct the urinary flow from the bladder to the exterior. As a rule they do not obstruct the passage of an instrument from the exterior into the bladder. A similar type of valve may extend proximally from the upper border of the verumontanum. The third form consists of a diaphragm across the lumen of the posterior urethra,
<i>Diaphragm</i>	

with a small perforation in it which allows a slow exit to the urinary flow.

The obstruction which these valves may produce is variable and consequently the age at which well marked symptoms develop may be from early infancy to manhood. The symptom-complex is that of chronic urinary obstruction resembling that in adults with acquired urethral stricture or enlarged prostate. The bladder first hypertrophies to overcome the obstruction but later begins to dilate, does not empty properly, and retains an increasing volume of residual urine. This is evidenced by increased frequency of micturition and distension of the lower abdomen. Sooner or later infection gains entry to the stagnant urine in the bladder and the symptoms increase, overflow incontinence of urine now being a feature. Meanwhile the kidneys and ureters, as a result of the increasing obstruction, begin to dilate and bilateral hydronephrosis and hydro-ureter appear. This is accompanied by a gradual failure of renal function with increasing uraemic symptoms.

*Symptoms**Residual urine**Infection**Hydro-nephrosis and hydro-ureter*

The complete picture in a child therefore includes dysuria, perhaps incontinence with symptoms suggesting chronic nephritis, nausea, vomiting, loss of weight, diarrhoea, and oedema. Chronic obstruction should be suspected on feeling a distended bladder or draining off a large volume of urine by catheterization.

Radiological examination, after intravenous injection of uroselectan B, will generally reveal the gross bilateral hydronephrosis and hydro-ureter. If the condition is far advanced, the kidneys may not excrete sufficient dye to outline the pelves and ureters, and in this event cystoscopy and retrograde pyelography should be performed. At the same time, a picture of the bladder, filled with the dye, should be taken, which will demonstrate the rather funnel-shaped neck of the bladder and dilated posterior urethra. Biochemical investigations reveal a high blood-urea and poor renal function tests (see p. 393).

*Diagnosis**Radiography**Biochemical*

The immediate treatment of an advanced case is similar to that of urinary obstruction in the adult, i.e. free drainage of the bladder until the kidneys have regained and stabilized their function. It is most important that the chronically distended bladder should not be emptied at one sitting; the urine should be let off slowly by catheterization and then suprapubic drainage instituted.

Treatment

The urethral obstruction may be dealt with when the renal function has recovered, but not before. The most satisfactory method is to remove the valves with a special small punch but it may be possible to excise them from the bladder through a suprapubic exposure.

Removal of obstruction

3.—MALE SEXUAL APPARATUS

(1)—Testis

1578.] Absence of a testis (anorchidism) is a rare anomaly and likely to be confused with imperfect descent or atrophy from inherited disease, such as syphilis. In some recorded cases, however, the testis, epididymis,

Absence

and a portion of the vas on one or both sides have been absent. The seminal vesicle and upper portion of the vas are generally present. This malformation is often associated with some other deformity, such as hypospadias or ectopia vesicae.

-dism Supernumerary testes have in rare instances been described; Boggon (1933) collected twelve examples, of which nine were on the left side. They are liable to be confused with the congenital cysts of the processus vaginalis.

rsion The testis is suspended within the scrotum by means of the spermatic cord and gubernaculum. In its normal position the epididymis and lower portion of the vas lie posteriorly and the upper pole of the testis is rotated slightly forwards. Any change in the position of the testis about its transverse axis is known as inversion. The commonest abnormality is a forward rotation on the transverse axis so that the epididymis comes to lie in front of the testis. The function of the gland is in no way interfered with and the condition does not give rise to any symptoms. It is only of importance clinically when the testis or epididymis becomes involved in some disease, such as tuberculosis, when an erroneous diagnosis may be suggested if the epididymis and testis are confused.

See also TESTIS, UNDESCENDED, Vol. XI, p. 671.

(2)—Hydrocele

See TESTIS AND CORD DISEASES, Vol. XI, p. 666.

4.—FEMALE SEXUAL APPARATUS

Abnormalities of the ovary are dealt with in the article OVARY DISEASES, Vol. IX, p. 319; of the uterus in UTERUS, DISEASES AND DISORDERS, p. 416; and of the vagina and external genitals in FOETUS DISEASES, MALFORMATIONS AND MONSTROSITIES, Vol. V, p. 365, and VULVA AND VAGINA DISEASES, p. 606.

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URTICARIA

See ALLERGY, Vol. I, p. 317; and
URTICARIA PIGMENTOSA, p. 410

URTICARIA PIGMENTOSA

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Reference may also be made to the following title:

SYPHILIS

1.—DEFINITION

(*Synonym.*—Xanthelasmaidea)

1579.] Urticaria pigmentosa is an uncommon disease consisting of chronic macules and nodules varying in colour between brown-yellow and brown-red. The lesions redden and swell, i.e. become urticarial, in response to friction. The malady most often starts in infancy but its development may be delayed until after puberty.

2.—AETIOLOGY

The cause is unknown. In the adult form there is often a history of toxic influences, but many patients appear perfectly healthy apart from the eruption. Morini believed that intestinal toxæmia, associated with hyperchlorhydria and eosinophilia, gave rise to sympathetic hypotonus. Although it is true that symptoms of intestinal toxæmia may accompany the efflorescence of the disease in some adult patients and that

*Relation to
toxæmia*

such symptoms may persist and be attended by superadded factitious urticaria, this view has not received strong support. The onset in Scolari's case was heralded by severe fever, generalized erythema, and oedema. Some patches of erythema disappeared entirely but others left macules of residual urticaria pigmentosa. At one time the lesions were identified with moles because of the pigmentation but this hypothesis is of historical interest only, and the records of onset after measles, chicken-pox, vaccination, or fright are examples of coincidence.

3.—MORBID ANATOMY

The histological picture shows an accumulation of cells in a fine and rarefied framework of connective tissue. These cells are mostly aggregated round the deeper blood-vessels and among them are usually many mast-cells. When oedema is present the lymph spaces are dilated. Melanin occurs in the basal layer, in the adjacent corium, and in the perivascular connective-tissue cells; sometimes a little pigment is found in the prickle-cell layer. Although most of the colour is due to melanin, haematin may be mixed with it in small quantities. It is said that the calcium and sodium chloride content of the blood is increased and that the coagulation time is shortened. Hollander described two children in whom the thymus gland was enlarged.

The mast-cells are the most interesting feature of the lesions. They may be present in large masses, as a diffuse infiltration, or as a slight increase, or they may be absent. They may be arranged in columns between the white fibrous tissue and may be so numerous as to constitute mast-cell tumours, in which the cells are often cuboidal as a result of pressure. It was originally thought that their presence was essential to the diagnosis but a few typical cases have been described in which no trace of them could be found (Quinquaud). The great majority of patients, however, show mast-cells in increased numbers, not only in the lesions but often also in the intervening apparently normal skin. Their significance is unexplained, for they do not show any numerical relation to the age of the patch, to the clinical type whether macular or nodular, to the depth or character of the colour, to the presence of any urticarial element, or to the degree of irritation. In those few cases in which the lymphatic glands are enlarged, mast-cells have been scattered through the gland, especially in the reticular tissue (Little). This lends some support to Fraser's view that these are 'tissue mast-cells', derived locally from connective-tissue cells or from lymphoid cells, and differing morphologically from 'blood mast-cells'. The same author has demonstrated by repeated biopsies that the numbers of these cells vary from time to time and that they may be temporarily absent.

4.-CLINICAL PICTURE

Nettleship described the first recognizable case in 1869, but attention was first drawn to the disease some six years later by Marrant Baker and Tilbury Fox. From that time until very recently it has been customary to divide the affection into congenital and adult types. Although this distinction is now realized to be artificial, it may be retained for the purposes of description.

- Infantile type* The infantile form of the disease is rarely congenital but the eruption starts within the first year of life in the great majority of cases and has usually become fully established before another twelve months have passed. The lesions either develop insidiously or appear in several showers with accompanying urticaria. Occasionally the first sign may be a wheal or a bulla. When the rash has appeared it may be purely macular, purely nodular, or may show mixed lesions. These vary in size in different cases but are fairly uniform in a particular patient, the average diameter being a quarter of an inch although nodules the size of a florin are not rare and a few have attained the dimensions of a five-shilling piece. They are rounded or ovoid and are usually distributed with their longer axes along the lines of cleavage so that they appear, for example, round the neck and parallel to the ribs. Each lesion has a definite outline and any irregularity in shape is extremely rare. The colour is striking and varies between a brownish-yellow and a deep brownish-red. On the trunk a buff, chamois-leather tint is most common, but the leg patches often show some lividity. The areas feel velvety and soft with some slight thickening in the more nodular patches. Their turgescence occurs after friction or may be excited by heat, emotion, or fever. This change is accompanied by congestion with increased reddening, urticarial swelling, and the formation of bullae in 5 per cent of cases. In spite of this repeated swelling the macules remain smooth and polished between the attacks, but the frequent stretching results in finely corrugated surfaces on the nodules. Factitious urticaria can nearly always be elicited on the intervening 'normal' skin.
- Number of lesions* The smallest number of lesions recorded is two, but they may be so copious that most of the skin is covered. They may even affect the buccal mucosa and the palate. In most cases the rash first appears on the trunk and when fully developed has usually spread only to the adjacent parts of the limbs. The face may be affected but the palms or soles only rarely. In the 'adult' form the lesions generally appear in early adult life as innumerable small freckle-like macules varying from one-eighth to one-quarter of an inch in diameter and chiefly affecting the trunk. The colour is usually mid-brown to dark brown and often contains a suggestion of purple, but the buff tinge present in children is never seen in older patients. The same tendency to turgescence and factitious urticaria is present.
- Lesions*
- 'Adult' type*
- Lesions*

Although most dermatologists have considered that the two types are

clinically distinct and did not recognize the adult picture as urticaria pigmentosa for many years, the careful researches of Hannay demonstrated beyond doubt that the two forms are identical. Thus, it was believed that the infantile type was always nodular and the adult type always macular, but both are mostly macular and the division into macular, nodular, or mixed forms is largely a matter of turgescence and chance. The clinical characters and distribution of the eruptions do not differ. Some children have borne only macules and some adults only nodules. The sex incidence in both types is the same, males slightly predominating. After the first year of life the incidence at different ages is fairly even and there is not any considerable increase at any other period of life, as might be expected if adult cases were a type apart. The symptoms also correspond. Itching is very variable although it is increased during a turgescence phase. Factitious urticaria may or may not be present. Gastro-intestinal symptoms may occur but in the vast majority of cases the general health is good and growth and nutrition are unimpaired.

*Comparison
of types*

5.—COURSE AND PROGNOSIS

It was once thought that all the infantile cases recovered spontaneously at adolescence. In many the rash gradually becomes less prominent and slowly disappears, but examples are on record which have persisted into adult life. Blumer's patient had suffered for forty years. In such cases the lesions tend to become less excitable and more definitely macular, showing the same picture as those which begin after puberty. Although the adult cases may take two years to attain their maximal efflorescence, thereafter they seem to persist unchanged throughout life except for a gradual lessening of the urticarial element.

6.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In infancy the disease may be confused, during its period of development, with urticaria or bullous lichen urticatus. The rapid acquisition of pigment and resistance to ordinary treatment serve to distinguish between them. When the colour is apparent, confusion is most likely to occur with multiple moles. In children with very few lesions and in whom the hairs of moles have not had time to develop, reliance must be placed on the turgescence or on biopsy. The lesions redden and swell so easily on slight friction that microscopy is really unnecessary. Xanthomatous deposits in children are rare and never numerous. The colour should not be confused as there is a difference in the quality of the yellow although the depth of colour in both diseases may vary greatly. Xanthoma is definitely hard to the touch unless it occurs in very thin infiltrations such as are seen in the eyelids.

*Diagnosis
from
urticaria and
bullous lichen
urticatus*

From moles

*From
xanthomatous
deposits*

In adult life the eruption is most often confused with secondary syphilis in spite of the great irritation. The patches, however, are not markedly infiltrated and none of the other signs of secondary syphilis, such as sore throat, are present. Also the lesions do not possess the curious ill-defined outline of the early syphilitic papules. Turgescence and the history will also aid the differentiation.

7.—TREATMENT

Any gastro-intestinal disturbance or factitious urticaria should be treated on appropriate lines, which generally dispose of these symptoms but do not affect the main eruption. Calcium salts, salicin, and X-ray therapy have been said to help but their value is extremely doubtful. No known treatment will disperse the disease although the use of antipruritic lotions, such as alkaline lotion of coal tar, and guarding against external and internal stimuli, may help to ameliorate the symptoms.

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UTERUS, DISEASES AND DISORDERS

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Reference may also be made to the following titles:

ABORTION

AMENORRHOEA

CANCER

CHORIONEPITHELIOMA AND HYDATIDIFORM
MOLE

CLIMACTERIC AND ITS DISORDERS

DYSMENORRHOEA

ENDOMETRIOSIS AND ADENOMYOMA

ENDOMETRITIS, CERVICITIS, AND METRITIS

FALLOPIAN TUBES DISEASES

LEUCORRHOEA

MENORRHAGIA AND METRORRHAGIA

PUERPERIUM

SEX HORMONES

STERILITY

I.—DEVELOPMENTAL ABNORMALITIES

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The scope of the above title demands that changes in the uterus should be considered by themselves, but the reader is reminded at the outset that abnormalities of the vagina are frequently combined with those of the uterus.

1.—NORMAL DEVELOPMENT

1580.] The uterus is formed by the fusion of the lower portions of the two Müllerian ducts which when fused are at first solid, canalization taking place later from below upwards. In the full-term female child at birth, the uterus tends to be C-shaped, and the cervical canal is longer than the cavity of the body of the uterus. Towards puberty the angle between the axis of the uterine cavity and that of the cervical canal widens, and the body of the organ increases in size more rapidly than does the cervical portion, so that the proportion is reversed, and the cavity measures one and a half inches compared with a cervical canal of one inch.

2.—AETIOLOGY AND CLASSIFICATION

Von Winckel's classification of uterine abnormalities offers a systematic explanation of the different types found. It depends upon what is normal

for the different stages of development of the organ. It is reproduced in modified form below.

Period 1: first month of intra-uterine life. The Müllerian ducts are formed as solid cords by the junction of the inner ends of the pronephric

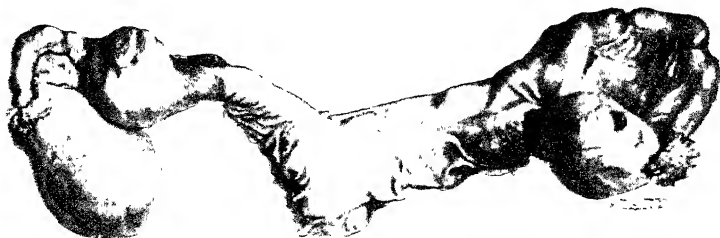


FIG. 28.—Rudimentary uterus
(This and Figs. 32 and 34 by courtesy of Professor D. Dougal)

and mesonephric tubules. Anomalies. (i) Both ducts may be absent (complete absence of the uterus). (ii) One duct may be absent (uterus unicornis).

Period 2: second month of intra-uterine life. The Müllerian ducts have united in part of their extent into the genital cord, and canalization

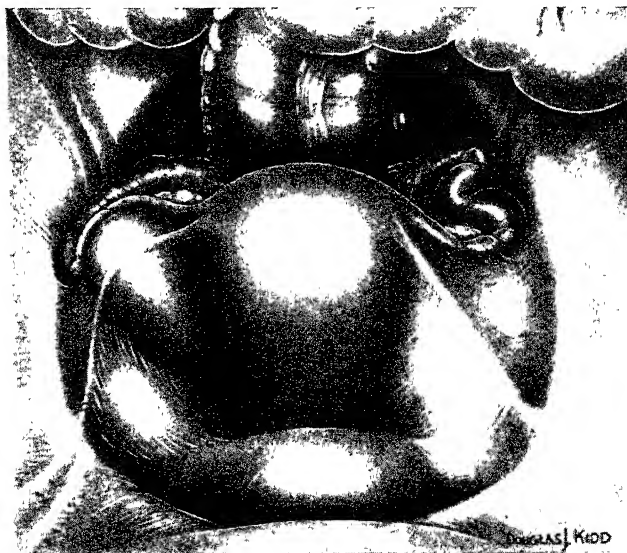


FIG. 29.—Accessory uterine horn

has begun. Anomalies. (i) The two ducts may remain completely separate (uterus duplex separatus, or uterus didelphys). In the most extreme degree of this there are two completely separate and fully developed genital tracts (Gemmell and Paterson). (ii) There may be absence of canalization of the separated or united ducts (uterus rudimentary, duplex, bicornis, or simplex) (see Fig. 28). (iii) There may be

partial canalization of the separated or fused ducts (uterus rudimentarius partim excavatus duplex, bicornis, or simplex). (iv) One duct may be

absent, the other present in an imperfect state (uterus unicornis cum rudimento cornu alterius).

Periods 3 and 4: third and fourth months of intra-uterine life. External fusion of the Müllerian ducts extends to the points of origin of the round ligaments, and the septum within gradually disappears.

Anomalies. (i) Uterus bicornis: septus, with

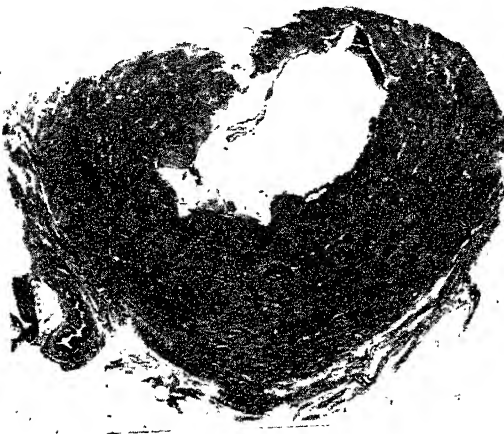


FIG. 30.—Transverse section of accessory uterine horn. $\times 4$

*Third and fourth month
foetuses*

Anomalies

a complete septum; subseptus, with a partial septum; or simplex, without any septum. (ii) Uterus introrsum arcuatus (septus, subseptus, and simplex). (iii) Uterus planifundalis (septus, subseptus, and simplex). (iv) Uterus foras arcuatus, i.e. uterus without a fundus (septus, subseptus, and simplex).

*Six to ten
months'
foetus*

Period 5: sixth to tenth lunar months of intra-uterine life. There is more marked development of the fundus. *Anomaly.* Uterus foetalis.

Anomaly

*First ten
years*

Period 6: first ten years of extra-uterine life. During this period the uterus is slowly losing its infantile characters. *Anomaly.* Uterus infantilis.

Anomaly

*Ten to
sixteen years*

Period 7: tenth to sixteenth years. The uterus develops from

Anomalies

the infantile to the mature organ. *Anomalies.* (i) Uterus virginens; (ii) uterus inaequalis; and (iii) hypoplastic uterus.

*Accessory
third horn*

In addition, a third Müllerian element may appear and form an accessory uterine horn (Ballantyne) (see Figs. 29, 30, and 31).



FIG. 31.—Endometrium of accessory uterine horn. $\times 150$

Clinical classification

The foregoing classification is scientifically accurate but too cumbersome for clinical purposes. The following is a useful working classification. (i) Absence of the uterus; (ii) unicorn uterus; (iii) bicornuate uterus (*a*) both horns equal in size and completely canalized, (*b*) horns unequal in size and or unequal in canalization (see Fig. 32); (iv) arcuate uterus; (v) infantile uterus; (vi) pubescent uterus (cochleate uterus or acute antelexion of the cervix); and (vii) hypoplastic uterus.

Various causes of failure of union of the two Müllerian elements have been described, no one of which accounts for all cases. (i) A vesico-

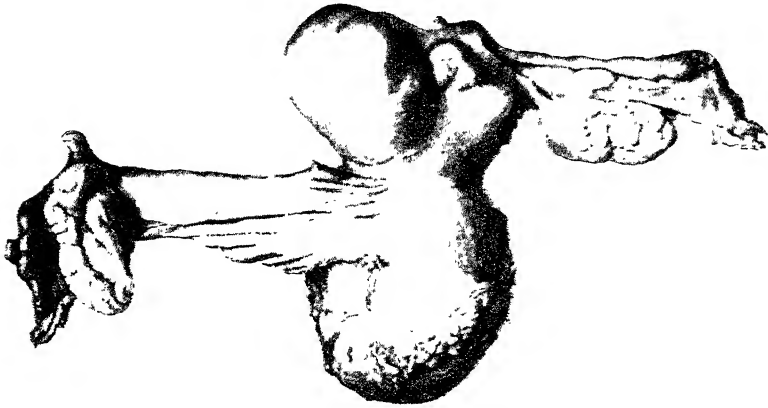
Pathogenesis

FIG. 32.—Bicornuate uterus with one normal and one rudimentary horn

rectal peritoneal fold of vascular origin may stretch across the pelvis from front to back and thus prevent union. (ii) The Müllerian ducts may be held apart by abnormally short round ligaments. (iii) Tumours may be present in the uterine muscle. In many patients no cause can be found for the abnormality.

3.—CLINICAL PICTURE

No one clinical picture will represent all cases. Some individuals undoubtedly go through life without any symptoms. In some the condition is only discovered during pregnancy or labour.

(1)—Non-Pregnant State

The incidence of these abnormalities is difficult to assess and often the condition is discovered accidentally during a pelvic examination and held not to be the cause of the symptoms. *Incidence*

In a gynaecological hospital which admitted 5,998 patients in three years, 14 patients had anomalies of Müllerian-duct development, but in only 3 cases (0.05 per cent of the patients treated) were these anomalies considered to be the cause of the patient's symptoms. During the same period 22 patients (0.36 per cent of the patients treated) showed

varying degrees of gross under-development of the uterus; this does not include the common cochleate uterus (see p. 435).

Absence of uterus

In the absence of the uterus there is complete amenorrhoea.

Unicorn uterus

The unicorn uterus does not cause any symptoms but may be associated with other severe congenital abnormalities.

Bicornuate uterus

The type of abnormality which gives rise to symptoms is that in which the horns are of unequal size and have inequality of canalization pre-

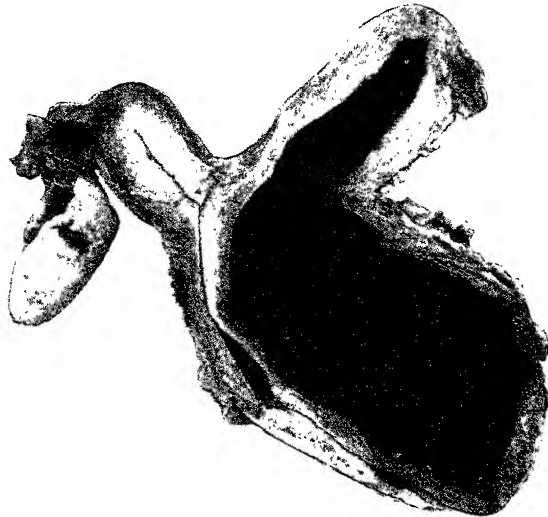


FIG. 33.—Uterus didelphys with unilateral haematocolpos

venting the easy outflow of menstrual fluid from one horn. Occasionally a uterus didelphys may be associated with a unilateral haematocolpos (see Fig. 33).

Clinical picture

These patients suffer from spasmodic dysmenorrhoea. The pain has usually been present since puberty and is felt in the lower abdomen, commonly in the hypogastrium and only occasionally on one or other side. It begins with the menstrual flow and lasts for a variable time, in some patients throughout the flow. It is usually severe enough to be incapacitating.

Physical signs

The physical signs are variable and may have to be elicited under anaesthesia as the patients are often virgin when they seek advice. At examination sometimes the presence of two vaginae or of a vaginal septum warns the examiner of the possibility of duplication of the genital organs. When there is no such warning the uterus is felt with a mass attached to it on one side. An undeveloped horn is attached to the better formed horn at a low level, i.e. at the level of the supravaginal cervix.



Radiograph after injection of iodized oil into bicornuate uterus

PLATE X

These physical signs may be interpreted as showing the presence of a fibroid or an endometrioma of the uterine wall. But, as the patients are usually under thirty years of age, and their symptoms have been present from puberty or soon after, the true diagnosis should be clear. Iodized oil may be injected into the uterus and a radiograph obtained (see Plate X). *Differential diagnosis*

Surgical treatment is essential and consists in the removal of the under-developed horn. Great care must be taken to secure haemostasis and complete peritonization. In operations on patients with double uterus, care is necessary to avoid injury to the ureter, which may be displaced. *Treatment*

Occasionally when the abnormality is lack of fusion of the upper parts of two well developed ducts (uterus bicornis unicollis) a plastic operation (utriculoplasty) may be undertaken to unite the horns. Successful pregnancies have followed this operation (Murray).

These remarks on bicornuate uterus also apply to the rare cases of an accessory third horn, in which instance the exact diagnosis will not be made until the

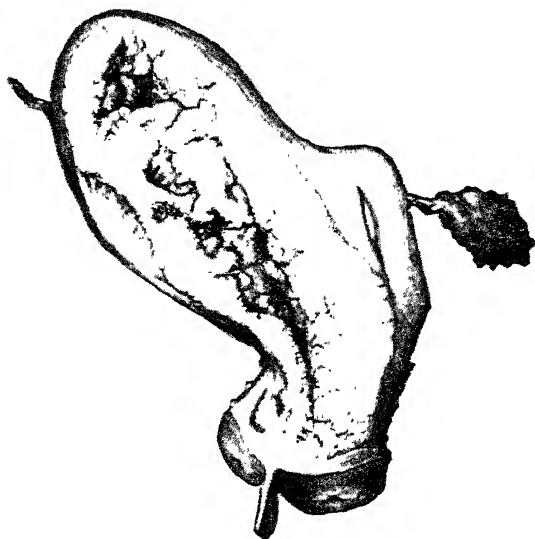


FIG. 34.—Carcinoma corporis in one horn of double uterus

abdomen has been opened and the relations of the round ligaments and appendages to the swelling thoroughly studied.

Patients who have some form of double uterus do not necessarily suffer from impaired fertility; they may show an unusually high percentage of twin pregnancies, possibly due to simultaneous pregnancies in the two horns. *Fertility*

Complications are remarkably rare. Doran and Lockyer stated that septate, bicornuate, and didelphic uteri were less liable to harbour tumours of clinical importance than were normal uteri. Buist and Valentine were able to collect from the literature only seven cases of carcinoma corporis in double uteri (see Fig. 34). *Complications*

Arcuate or septate uterus

This type of abnormality does not as a rule give rise to any symptoms unless pregnancy occurs, although it may occasionally be a cause of menorrhagia. In such cases the diagnosis of fibroid is usually made, and the true diagnosis is only reached on opening the abdomen. The treatment is utriculoplasty.

Infantile, pubescent, and hypoplastic uteri

Infantile, pubescent, and hypoplastic uteri may not give rise to any symptoms. Sometimes dysmenorrhoea is a complaint (see Vol. IV, p. 355). Sterility is another complaint and may be treated by administration of oestrin with the aim of stimulating fuller development of the uterus. It should be given in the form of oestradiol benzoate, 5 mgm. twice a week, or stilboestrol 1 mgm. twice a day, for three weeks following menstruation, and then a week's rest. Dilatation of the cervix with insufflation of the uterine (Fallopian) tubes will assist conception in about one-third of the cases of pubescent uteri.

(2)—Pregnant State

*Clinical
classification*

Clinically two main types of uterine abnormality have to be considered: (i) those with one horn underdeveloped (uterus unicornis cum rudi-



FIG. 35.—Pregnancy in rudimentary horn of bicornuate uterus; the pregnant horn is ruptured. (From a specimen in the Gordon Museum, Guy's Hospital. From *A Short Textbook of Midwifery*, by G. F. Gibberd)

mento cornu alterius, or uterus bicornis cum cornu rudimento of some authors; rudimentary horn); and (ii) those with both horns equally, or nearly equally, developed (uterus bicornis).

Rudimentary horn

Pregnancy

Munro Kerr stated that pregnancy was very rare in a uterus unicornis and gave details of the relations of the different forms of uterine abnormality to pregnancy and labour. Pregnancy in the rudimentary horn of a uterus often terminates by rupture of the rudimentary horn (see Fig. 35), and is then accompanied by the symptoms and signs classically associated with an extra-uterine pregnancy. (See FALLOPIAN TUBES DISEASES, Vol. V, p. 258.) The accident, however, occurs at a somewhat later stage of pregnancy than those in which the ovum is in the Fallopian tube. In a few recorded cases pregnancy in a horn of this type has persisted till full term. The termination has been intra-uterine death some time after calculated term and the foetus has had to be removed by abdominal section.

Diagnosis

The diagnosis is apt to be mistaken for that of pregnancy in a fibroid

terus, but the signs of internal haemorrhage call for laparotomy, when the real condition is disclosed.

When the abdomen has been opened the rudimentary horn must be removed but whenever possible the ovary on the affected side should be conserved. *Treatment*

True bicornuate uterus

Pregnancies in bicornuate uteri are liable to terminate early. Miller found that in 67 pregnancies there were 19 abortions and 7 premature labours. The abortions are liable to be incomplete, and infection is therefore common either demanding immediate treatment or leading to menorrhagia later. The decidua may be retained in the unimpregnated horn, and this too may lead to menstrual disturbance. According to Polak the proportion of twin pregnancies is high. *Premature labour and abortion*

It has been often stated that bicornuate uteri cause transverse lies in pregnancy. Such a lie should suggest this uterine abnormality in a primigravida with a normal pelvis and normal foetus. It may be treated by external cephalic version and the application of a binder during pregnancy. Figures quoted below do not support this as a common effect. *Abnormal presentation*

Many patients pass through pregnancy and labour without any abnormality or sign of dystocia. Certain eventualities, however, are recognized. *Labour*

In the first stage of labour there is not as a rule any abnormality, but when there is a twin pregnancy with one foetus in each half of the double uterus there is liable to be inertia of the second half to be delivered. *First stage*

In the second stage the non-pregnant half of the uterus may lie below the presenting part of the child and cause obstruction. On the other hand it has been stated that abnormally wide pelvis are commonly associated with this condition. Lockyer, however, pointed out that in 84 collected cases there was only one abnormally wide pelvis. In the third stage retention of the placenta occurs. Miller noted that manual removal of the placenta was necessary 8 times in 41 cases. *Second stage*

An attempt has been made to assess the incidence of the various abnormalities of labour produced by congenital uterine defects from a study of the clinical reports of twelve large maternity hospitals or units. The figures must be taken only as a rough index and not as statistically accurate. *Third stage*

The total number of deliveries covered by these reports is 288,582, and congenital abnormalities of the uterus are recorded 49 times, i.e. 1 in 5,890 labours, or 0.017 per cent. The abnormality caused difficulty, however, on 27 occasions only, i.e. 1 in 10,688 labours, or 0.009 per cent. The non-pregnant horn obstructed labour in 11 patients, 3 of whom had had previous normal labours, and for these patients Caesarean section was undertaken. In another patient with this complication laparotomy was performed and the non-pregnant horn lifted out of the pelvis; a normal labour occurred twenty-four hours later. In 5 patients the non-pregnant horn also contained fibroids and therefore Caesarean section was performed. A contracted pelvis was also present in 3 patients and provided the indication for Caesarean section. *Frequency of the various complications*

Methods of treatment

Tabulation of Complications of Labour Associated
with Congenital Uterine Abnormalities

TYPE OF ABNORMALITY	NO. OF CASES	COMPLICATIONS	TREATMENT
(a) In the following cases the uterine abnormality was responsible for the difficulty in labour:			
Bicornuate uterus	11	Obstruction of labour by non-pregnant horn	Caesarean section
Bicornuate uterus	1	Feared possibility of obstructed labour	Laparotomy. Non-pregnant horn lifted out of pelvis. Normal labour 24 hours later
Bicornuate uterus	1	Feared possibility of obstructed labour	Non-pregnant horn pushed up out of pelvis in each of two pregnancies in the antenatal period. Normal labour on each occasion
Bicornuate uterus with fibroids	5	Obstruction of labour by fibroids in the non-pregnant horn	Caesarean section
Bicornuate uterus with transverse lie	3	Disproportion due to lie of child	Caesarean section
Bicornuate uterus with abnormal presentations	4	Difficulty due to the abnormal presentation	Treatment appropriate to the abnormal presentation
Bicornuate uterus	2	Retention of placenta	Manual removal of placenta
Total		-	27
(b) In the following cases the uterine abnormality was not the cause of the difficulty in labour:			
Bicornuate uterus with contracted pelvis	3	Disproportion due to the contracted pelvis	Caesarean section
Unicorn uterus and pelvic kidney	1	Obstruction of labour by pelvic kidney	Caesarean section
Unicorn uterus and obliquely contracted pelvis	1	Disproportion due to contracted pelvis	Caesarean section
Total		-	5

The assistance rendered by Dr. O. G. Bark in searching the
Hospital Reports is gratefully recorded.

A unicorn uterus with an additional complication was found in 2 patients (1 pelvic kidney and 1 obliquely contracted pelvis), and in them also delivery was by Caesarean section.

In contrast to the above, 2 other cases may be cited: (i) a patient known to have a bicornuate uterus had six normal, and no complicated, deliveries; and (ii) another patient had the non-pregnant horn pushed up out of the pelvis in each of two pregnancies during the antenatal period, and on each occasion delivered herself successfully.

Abnormal positions of the child were the cause of some difficulty in 7 patients; in only 3 of these (2 primigravidae and 1 multigravida) was the lie transverse and all of these were delivered by Caesarean section. The other 4 patients were delivered vaginally by the usual methods appropriate to the abnormality of the position found.

Retention of the placenta occurred only twice, once in a primigravida and once in a multigravida who had previously had three abortions and one premature and two normal deliveries. This patient suffered from retention of the placenta three times in all.

Among the patients delivered normally, and not included above, one had previously had uteruloplasty performed for a bicornuate uterus. The essential points illustrated by the above cases are summarized in the table on the opposite page.

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II.—DISPLACEMENTS

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I.—NORMAL POSITION

1581.] Knowledge of the normal position and relations of the uterus is necessary for a clear understanding of its displacements. Within limits the uterus is a mobile organ and has a fairly extensive range of movement when acted on by forces external to it, but it tends to return to the normal position when those forces have ceased to act. That position is determined mainly by the attachments of the cervix. On

either side the cardinal ligaments, strong bands of fascia, run outwards and backwards in the lower part of the broad ligament, closely following the line of the uterine arteries, attached in front just above the junction of cervix and vagina, and spreading out posteriorly to merge into the parietal pelvic fascia. *Cardinal ligaments*

The uterus is thus supported in the middle of the pelvis with the cervix at the level of the ischial spines; it may be compared to a child sitting on a swing, because it can be drawn forwards or pushed backwards or from side to side; if the swing ropes are slack there is descent, if they are tightened up there is fixation. And just as the child can lean forwards or backwards on the swing, the body of the uterus can rotate backwards or forwards on the cervico-vaginal junction. *Mobility of uterus*

Normally the axis of the uterine body is inclined slightly forwards on that of the cervix (anteflexion), and the pull of the lateral attachments of the cervix is so directed that the body of the uterus is thrown forwards against the posterior and upper aspect of the bladder (anteversion). *Anteflexion Anteverision*

The maintenance of this position is materially assisted by the action of the anterior parts of the levatores ani muscles. Normal tonic contraction of these fibres, acting primarily on the vagina and rectum and indirectly on the cervix, tends to push the cervix upwards and backwards and so to tilt the body of the uterus forwards. Active contraction of these muscles is usually a combined muscular movement, the muscles of the abdominal walls contracting at the same time, as in coughing, straining, and defaecation, and is an important factor in preventing displacement of the uterus during such expulsive movements. *Levatores ani*

II.—DISPLACEMENTS

1582.] The uterus being so mobile is easily displaced. A full bladder may push it backwards; a loaded rectum and sigmoid may raise it. Morbid conditions may cause grotesque displacements, which are of secondary interest but emphasize the view that the uterus is within limits a very mobile organ, and that a deviation from the normal position should not always be looked on as an indication for gynaecological orthopaedics.

1.—RETROVERSION

Next to prolapse retroversion is the commonest and the most important form of uterine displacement. The uterine axis normally forms about a right angle with that of the vagina. In retroversion it is rotated backwards, with the result that it may come into line with the vagina or even form a re-entrant angle with it. There are two distinct types of retroversion, the congenital or developmental and the acquired, which require different treatment. *Uterine axis*

(1)—Congenital or Developmental

(a) *Aetiology*

This type is commonly found in nulliparous, often virgin, women; it may be associated with symptoms, dysmenorrhoea and/or sterility, or may be discovered in the course of a complete physical examination without any symptoms referable to the genital system. The condition is in all probability due to failure of the uterus and vagina to reach full development at the time of puberty. The uterus, often rather small, lies in the axis of the vagina but moves freely in the pelvis.

(b) *Clinical Picture*

It is doubtful if this condition causes symptoms. Failures of adequate development, such as this condition, a conical cervix, a pin-hole os, and an acute antelexion, are undoubtedly associated in many cases with symptoms, usually dysmenorrhoea and/or sterility. On the other hand, many women with such abnormalities lead normal sexual lives and become mothers. In the absence of genital symptoms, it is quite unjustifiable to explain the symptoms of a neurotic or neurasthenic patient by informing her that her womb is out of place and so giving her the fixed idea that she is not as other women are. If she is told of the position of her uterus she should be reassured; her retroversion is probably not more important from a medical point of view than the possession of a snub nose. If the patient complains of dysmenorrhoea and/or sterility, the treatment appropriate for these symptoms should be given.

(2)—Acquired

(a) *Aetiology*

A normal uterus may be displaced backwards by many causes. An ovarian tumour perched on the brim of the pelvis, post-menopausal weakening of the uterine supports in elderly women, beginning or established prolapse, the pull of adhesions after pelvic peritonitis, and the development of an endometriosis may be associated with retroversion, but the position of the uterus is in these cases an unimportant incident.

Claims are sometimes made that a fall on the buttocks has caused backward dislocation of the uterus. The history is usually that there was a feeling of something going out of place internally at the time, and that the accident has been followed by backache or discomfort. The likelihood of such an accident would be increased if the uterus were enlarged by an early pregnancy, and I have seen a case in which it was claimed that a miscarriage had been thus caused. The possibility of such an accident cannot be denied, but a careful examination is necessary to establish the fact that a retroversion exists and, so far as is possible, to exclude the probability that it was already present before the accident.

(b) Clinical Picture

The following description concerns chiefly the type of retroversion which occurs after child-birth and is associated with symptoms: back-ache, often worse before menstruation, leucorrhoea, and heavier menstrual losses. On examination retroversion of the uterus is easily detected. The fundus is felt in the posterior fornix, but it does not as in developmental retroversion move freely in the pelvis; it rests on the pelvic floor. It is bulky, rather flabby, and often tender on palpation. It may be easily replaced; but this may be difficult, sometimes because the uterus is fixed by adhesions; but more commonly it is due to the bulk of the uterus, to slipping of the fundus between the uterosacral ligaments forming the upper lateral limits of the recto-uterine excavation (pouch of Douglas), or the fact that the patient, because her uterus is tender, does not permit pressure upon her fundus adequate to dislodge it from the recto-uterine excavation. A retroversion should not be considered 'fixed' until an attempt to replace it has been made under an anaesthetic.

*Retroversion
after
child-birth
Symptoms
Signs*

This type of retroversion is not uncommonly associated with retroflexion, when the body of the uterus has sagged backwards on the cervix and the abnormal position of the fundus is consequently exaggerated. In extreme cases the uterus is upside down, the external os being the highest point and the fundus the lowest when the patient is in the dorsal position. The displaced fundus may, through the ligaments of the ovaries, drag the ovaries down into the recto-uterine excavation, and the prolapsed ovaries may cause pain on defaecation or in coitus. The displacement may also be associated with some degree of uterine prolapse. In this condition care should be taken to examine the cervix, which will often be found torn, with exposure of an inflamed cervical mucous membrane (ectropion), or instead of the normal stratified epithelium covering the vaginal portion there may be some areas of inflamed epithelium of the cervical canal type (granular cervix or inflammatory erosion). In view of the trauma suffered by the cervix during the first and second stages of labour, it is not surprising that the injured tissues should sometimes become infected after delivery, and that the infection should sometimes be chronic.

*Associated
lesions
Retroflexion
Oophorangi
Uterine
prolapse
Cervix
Ectropion
Erosion
Cervicitis*

The normal process of involution concerns not merely the uterus but the soft tissues of the pelvis generally, including the uterine supports and the levatores ani muscles. Involution is delayed or prevented by acute puerperal infection; therefore it is reasonable to conclude that the milder and more chronic infections just mentioned are largely responsible for the slack ligaments and atonic muscles which fail to maintain the bulky uterus in anteversion. Indeed the cervical lesion alone would account in many cases for the symptoms usually regarded as the classical symptoms of retroversion.

Involution

(c) *Diagnosis and Differential Diagnosis*

In this there is not usually much difficulty. The fundus cannot be palpated in the anterior fornix but can be felt in the posterior, and the greater the displacement the easier as a rule is the diagnosis. Four stages are often described, but these are arbitrary and cannot be regarded as guides to treatment. It is more important to ascertain whether (i) the uterus is bulky and tender; (ii) cervical lesions are present; (iii) the uterus is replaceable (an anaesthetic may be required to decide this point); (iv) the ovaries are prolapsed and tender; and (v) there is beginning prolapse of the uterus.

Errors in diagnosis can be made, because not every tumour felt in the posterior fornix is necessarily the fundus of the uterus, even when that cannot be palpated in front. Confusion may be due to a fibroid in the posterior wall of the uterus, an inflammatory mass, a tubal mole lying in the recto-uterine excavation, or a prolapsed and adherent ovary. It may be impossible to define the position of the fundus in a patient with a thick or rigid abdominal wall. An examination under an anaesthetic may be necessary in doubtful cases.

(d) *Treatment*

Acquired retroversion can best be treated if it is discovered early, e.g. at a routine postnatal examination some six weeks after confinement, but most cases come under observation when the displacement has been present for months or even years.

Treatment of cervical lesion

If a cervical lesion is found it should be treated first. Usually cervical inflammations yield to antiseptic measures, e.g. swabbing with a 3 per cent solution of trinitrophenol in alcohol, liquefied phenol, iodized phenol, a 10 per cent solution of silver nitrate, a 2 per cent solution of mercurochrome, and a 1 per cent solution of acriflavine. The treatment, which may be carried out once or twice a week, is assisted by the introduction after each swabbing of a tapon of ichthammol (10 per cent in glycerin) or of iodine (1 per cent in glycerin) to be removed in 12 to 24 hours. This treatment may be continued up to six weeks. If the case is refractory, diathermy or curettage of the affected area may be tried. Excision or excision combined with suture of a laceration may be required. In some cases the uterus resumes its normal position and this is followed by cure of the cervical inflammation and the consequent recovery of tone in the soft tissues of the pelvis.

Replacement of the uterus

Even when a cervical lesion is not present, the uterus may be retroverted and may require replacement. The manoeuvre may be assisted by placing the patient in Sims's position with a cushion under the buttocks, or in the knee-chest position, because in these attitudes the force of gravity assists the efforts of the operator. Anaesthesia with complete muscular relaxation allows more thorough manipulation and

practically abolishes the influence of abdominal pressure which tends to press the retroverted organ down into the recto-uterine excavation. Therefore if the patient has been anaesthetized for diagnosis or treatment, the opportunity should be taken to effect replacement of the uterus.

The classical method is to pass two fingers into the posterior fornix, to raise the fundus out of the recto-uterine excavation, and to grasp it by the hand on the abdomen. The pressure of the fingers in the vagina is then transferred to the front of the cervix, and, the fingers pushing the cervix backwards and pulling the fundus forwards, the uterus is anteverted. *Technique*

The following method of replacement is very effective: the patient is anaesthetized and in the dorsal position. The cervix is grasped with volsella, drawn down to the entrance of the vagina, and then depressed and carried backwards into the posterior fornix, while the posterior vaginal wall is strongly retracted with a speculum. After this manoeuvre complete reposition can be effected bimanually. When the uterus cannot be replaced under an anaesthetic, it is almost certain that it is bound down by adhesions. *Another method*

Pessary treatment for retroversion

The pessary is definitely useful in the treatment of retroversion, but it should not be used indiscriminately. Improper use of it may even aggravate symptoms; it may cause pain by pressure on a tender unreplaced fundus or on a prolapsed ovary and, if the cervix is inflamed, it may by its presence in the vagina increase discharge and delay healing.

A pessary should not be introduced if active inflammation is present, or if the uterus has not been or cannot be replaced. It is a temporary expedient to support the uterus in its normal position until the soft tissues have recovered tone. It should not be used in cases of congenital retroversion, in which it may produce leucorrhoea but cannot permanently affect the displacement. *Contra-indications*

The type of patient likely to benefit from wearing a pessary is one who has not completely recovered from a confinement, or who from any other cause is flabby and has muscles lacking in tone and who may be reasonably expected to recover strength under appropriate treatment. The pessary will maintain the normal position of the uterus until the patient's soft tissues are in condition to do so. *Indications*

The pessary commonly used for retroversion is the Hodge or Hodge-Smith. The uterus should first be replaced and the size of pessary suitable estimated by measuring with the finger the length of the vagina. It is better to select for a first trial a pessary too small rather than one too large. Introduction is effected with the plane of the pessary, narrow end first, in the oblique diameter of the vaginal orifice, so that the anterior bar lies to one side of the sensitive urethral orifice. If there is difficulty in introduction, more room can be gained by depressing the perineum. When the instrument has passed into the vagina, the forefinger follows *Technique*

it up and carries the inner end up behind the cervix. A bimanual examination is then made to ensure that the uterus is anteverted. If the pessary fits correctly, there should be just room for the forefinger between it and the back of the symphysis pubis, it should not be displaced on coughing or straining, and the patient should feel comfortable.

The patient should be kept under observation for the first month to make sure that her uterus is maintained in anteversion. She should use a vaginal douche twice or thrice a week. A solution of sal antisepticus or dettol considerably diluted is suitable. At the end of six months the pessary may be removed, and the patient should be examined a month later to see if the uterus remains in position.

Operative treatment

Operation for retroversion is not so common as it was some years ago, gynaecologists now considering that a retroversion without symptoms does not indicate operation, and that when symptoms are present they should be logically presumed to be due to the displacement before an operation is recommended. When, however, treatment as already outlined has proved ineffectual, the question of operation must arise. It must also be faced when the uterus is irreplaceable or the ovaries are prolapsed and tender, when there is evidence of pelvic inflammation or of endometriosis, or a history of repeated abortions.

The operation usually practised is that known as Gilliam's or one of its many modifications. The guiding principle of the operation is to use the round ligaments as riding-cables attaching the fundus to the anterior abdominal wall.

The technique as originally described is as follows. After the abdomen has been opened, a puncture wound is made through the rectus sheath, rectus muscle, and peritoneum on either side about $1\frac{1}{2}$ to 2 inches from the middle line and about 2 inches above the symphysis; forceps are passed through the wound; the slack of the round ligament is seized and drawn through and fixed in front of the rectus sheath so that the fundus is held in anteversion.

Various modifications since introduced concern details of technique, but the principle of the operation remains the same. One of its great advantages is that it in no way interferes with the course of a subsequent pregnancy. Many other operations, most of them now of historic interest only, have been devised for the cure of retroversion. Ventral suspension gave the uterus a fundal ligament by stitching the fundus to the peritoneum of the anterior abdominal wall. Ventral fixation incorporated the fundus in the anterior abdominal wall by fixing it between the recti muscles and was used mainly in the treatment of prolapse in women past the menopause. Vaginal fixation was and still is sometimes used in the same type of case. An incision is made through the anterior fornix, the bladder separated from the anterior vaginal wall, the vesico-uterine reflexion of peritoneum opened, and the fundus brought forwards and interposed between the base of the bladder and the vagina. The Alexander-Adams operation utilized the round liga-

ments but dealt with them without opening the abdomen. The inguinal canals were opened on each side and the round ligaments isolated, pulled forwards so as to bring the fundus into anteversion, and fixed in that position. *Alexander-Adams operation*

Operation for suspension of a retroverted uterus should be preceded by operative treatment of any disease or injury of the cervix and, in cases of prolapse, by a colpoperineorrhaphy. It may be necessary to supplement the operation by shortening of the suspensory ligaments of the ovaries to relieve prolapse, possibly by resection of the ovaries, and by an appendicectomy.

Before recommending operation it should be borne in mind that many a woman with a retroverted uterus leads a normal sexual life, bears children, and reaches the menopause without undue discomfort.

(3)—Effect of Retroversion on Pregnancy

Pregnancy occurs in a retroverted uterus probably almost as readily as in one more normally placed.

(a) *Spontaneous Rectification*

The gestation often runs a normal course: the fundus at about the twelfth to the sixteenth week rises out of the pelvis and reaches its normal position at the pelvic brim. This rectification may occur suddenly in the interval between two examinations. It may be encouraged by directing the patient to assume the knee-elbow position for five minutes on going to bed and again on rising in the morning.

(b) *Replacement*

When an early pregnancy has been diagnosed in a retroverted uterus, the patient should be warned of the risks of the condition and kept under close observation during the critical period from the twelfth to the sixteenth week. If rectification has not taken place spontaneously by the end of the fourteenth week, an attempt at manual replacement should be made with the patient in Sims's position or in the knee-chest position. Replacement is much more easily effected if the patient is anaesthetized. It may be impossible owing to adhesions binding down the fundus, and an abdominal operation may then be required. *Replacement*

(c) *Persistent Retroversion*

The retroverted gravid uterus which remains in its abnormal position is a well known clinical entity and causes unfortunate complications as pregnancy advances.

(i) *Abortion*

The coincidence of a retroversion with abortion about the twelfth to the sixteenth week is so well established as a clinical observation that it is difficult to deny a causal connexion between them. If the case is seen in the stage of 'threatened abortion' with slight loss and without pains, an attempt should be made, if necessary under an anaesthetic, to replace the uterus, and the patient should then be put to bed and *Threatened abortion*

given sedatives. If smart hæmorrhage, pains, and dilatation of the cervix show the abortion to be 'inevitable', the uterus should be cleared out and the retroversion treated subsequently.

(ii) *Retention of urine*

When the fundus of the gravid uterus remains in the recto-uterine excavation, the growth of the organ carries the cervix upwards behind the symphysis, and in its ascent it pulls on the anterior vaginal wall. The tension compresses the urethra in its course through the vaginal wall, just as the lumen of a rubber tube is narrowed by pulling on it; or the cervix may come forwards and nip the urethra against the back of the symphysis.

There is at first difficulty in micturition, leading very shortly to complete retention. This is followed by the formation of an abdominal tumour, the distended bladder, which often reaches the umbilicus. By this time there is commonly overflow with dribbling, and cases have been recorded in which the continued pressure has caused sloughing of the bladder mucosa.

Diagnosis is not difficult. The abdominal tumour may cause momentary hesitation, but the history of pregnancy and a vaginal examination can leave no doubt, and the passage of a catheter clinches the diagnosis. Catheterization is not always easy, because the urethral orifice is often drawn up behind the symphysis and is not easily found.

These patients are said to do well if kept in bed and catheterized regularly. I prefer, after emptying the bladder, to replace the uterus, if necessary under an anaesthetic. A pessary may be inserted after reposition to give a sense of security, but I have never seen a replaced uterus show any sign of sinking again into retroversion, and every day of the pregnancy lessens the possibility of its doing so.

(iii) *Pregnancy proceeding to term in a fixed retroverted uterus*

This rare complication has been reported. The ovum is accommodated in the ballooned-out anterior wall of the uterus, and the posterior wall shares in the uterine hypertrophy but remains folded on itself in the pelvis and, when labour comes on, lies in front of the presenting part. The condition gives rise to difficulty in diagnosis and to obstruction to delivery, which may necessitate Caesarean section. I have never seen this condition, but I have twice operated for an analogous condition—fixation of the fundus low down on the anterior abdominal wall with a thickened and folded anterior uterine wall which was obstructing delivery; one of these patients had undergone an Alexander-Adams operation some years before for retroversion.

2.—ANTEFLEXION

1583.] Strictly speaking this is not a displacement but rather an internal derangement of the uterus. There is an exaggeration of the normal forward inclination of the body upon the cervix, often associated

with an underdeveloped cervix—the 'cochleate uterus'. The condition is due to failure of the uterus to develop normally at puberty. It may not cause any symptoms or may be discovered during examination of a patient with dysmenorrhoea and or sterility. *'Cochleate uterus'*

The diagnosis can best be made with the patient under an anaesthetic and may be followed immediately by dilatation and the introduction of a sea-tangle tent. The passage of the dilators may be difficult, and the internal os may need some search. An injudicious display of strength may easily push the dilator through the uterine wall at the angle. Sea-tangle tents may give some trouble in removal. They are firmly gripped at the internal os, and the grip may not relax for two or three days, but they may be safely retained for that time. Only a gentle pull should be made to remove them; a first trial may be made after 24 to 36 hours. If much force is used, the lower end of the tent may be broken off, and an incision of the cervix may then be required to remove the portion left in the uterus. *Diagnosis*

3.—OTHER DISPLACEMENTS

1584.] That common and important form of displacement, descent of the uterus or prolapse, is dealt with on page 436. There remain to be mentioned certain displacements due to the pushing or to the pulling of a very mobile organ from its ordinary position by a number of forces, some physiological, some pathological. The cause in these conditions is much more important than the effect. *Prolapse*

(1)—Ascent

Thus the uterus may be raised into the abdominal cavity (ascent) by its own enlargement (pregnancy or fibroid), by a growing tumour, e.g. an ovarian cyst, to which it is adherent, or it may be pushed up by a tumour from below, as happens in the development of a haematocolpos due to an imperforate hymen.

(2)—Lateral Displacement

This may occur owing to the push of a tumour or of an inflammatory mass or may follow the formation of cicatricial tissue after the subsidence of a pelvic inflammation.

(3)—Torsion

This has been very rarely reported. The organ is usually the seat of a tumour, and a hysterectomy would seem to be indicated.

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III.—PROLAPSE

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1.—DEFINITION

1585.] Used correctly, the term prolapse of the uterus means descent of the uterus but in common practice it is synonymous with 'genital prolapse' and includes cystocele, rectocele, and stress incontinence as well as true prolapsus uteri. These four conditions are all parts of genital prolapse; they are due to the same causes, are cured in the same way and, although in any case one may be more marked than the others, one rarely, if ever, occurs without at least one of the others.

2.—AETIOLOGY

*Anatomical
features
Pelvic floor*

Parametrium

It is now generally accepted that the female pelvic organs are maintained in position by the pelvic floor. A plane of muscular and connective tissue forms a concave floor to the pelvis, stretching from its pelvic attachments in well defined bundles and perforated in the middle line by the urethra, vagina, and rectum, along each of which it is prolonged and attached. In the bottom of this depression is a mass of connective tissue and unstriped muscle, the parametrium, collected chiefly around the upper part of the vagina and cervix, but extending forwards in the uterovesical folds to support the bladder and anterior vaginal wall and backwards in the uterosacral ligaments to support the rectum and posterior vaginal wall. This combination of pelvic muscle and parametrium constitutes the pelvic floor.

That the pelvic floor is the sole support of the uterus is shown by every panhysterectomy. Cutting the broad and round ligaments does not increase the mobility of the uterus but as soon as this tissue around and below the uterine artery is severed the uterus can be moved a considerable distance. This tissue suspends the uterus and supports the bladder, rectum, and vaginal walls, and these structures can descend only when the pelvic floor is overstretched, torn, or otherwise weakened. The descent may be hastened by other factors such as increased abdominal pressure from chronic coughing, tumours, heavy work, increased weight of the uterus from fibroids or subinvolution, or increased weight of the cervix from fibroids or chronic cervicitis.

Causes of descent of pelvic organs

Parturition is the commonest cause of weakness of the pelvic floor, and genital prolapse therefore occurs most often in parous women; in a small percentage of cases it occurs in nulliparae as the result of some developmental weakness of the pelvic floor on which is superimposed one of the secondary causes, generally hard physical work. For this reason prolapse in virgins is commoner in the industrial north of England, where girls do heavy work in the mills, than in the south.

Causes of weakness of pelvic floor

3.—CLINICAL PICTURE

The patient complains of a 'bearing down', or that 'something comes outside or into the passage', or that 'water comes away when she strains or stoops', or that she has 'aching pain in the lower abdomen or back when she works', or that 'a lump comes down when she strains at stool'.

Examination shows either the whole uterus outside with the vaginal walls completely everted—procidentia; bulging of the anterior vaginal wall on straining—cystocele, though this term is only strictly correct if the bladder wall is attached to this bulging vaginal wall; spurts of urine when the patient strains—stress incontinence; bulging of the posterior vaginal wall on straining—rectocele, though this term, also, is correct only if the rectal wall is adherent to the bulging vaginal wall; or descent of the cervix on straining—prolapse of the uterus.

Types of cases

4.—TREATMENT

As every case can be cured by operation, palliative treatment by means of pessaries is justifiable only (i) when the patient's general condition will not allow any operation, or (ii) when the patient is young and intends to have further children in the near future. Age alone is no contra-indication to operation. I often perform colporrhaphies on women over 70 years of age. Even if a pessary makes the patients comfortable at first, increasing senile atrophy renders this more and more difficult and many women come to be cured by operation after many years of only partial relief from a pessary with its attendant discomforts.

Methods of treatment

Effect of operation on future pregnancies

Colporrhaphy does not increase the difficulties or dangers of subsequent confinements, rather the reverse, but the prolapse recurs in about 25 per cent of cases. In the case of a young woman, who intends to have more children in the near future, it is therefore justifiable to insert a well fitting rubber-covered watch-spring pessary and defer operation until she has completed her family. Many of these patients, however, dislike pessaries and find the symptoms so much increased during pregnancy, even if they are comfortable at other times, that they prefer the certainty of comfort which an operation gives even with the risk that it may have to be repeated after another confinement.

Treatment of old women

Old women, physically unfit for operation, may be made comfortable with a rubber-covered watch-spring pessary or may require some form of cup-and-stem pessary supported by a waist-belt. Pessaries are at their best unsatisfactory and should rarely, if ever, be required as the unfit patient should have had the genital prolapse cured when she was in good physical condition.

Operations

Operations devised for the cure of this condition are legion and the literature has reached colossal proportions. Those most commonly performed can be divided into five classes: (i) abdominal fixation with or without colporrhaphy; (ii) hysterectomy; (iii) vaginal interpositions; (iv) Le Fort's operation; and (v) colporrhaphy.

Abdominal fixation

Abdominal fixation by itself is useless in the treatment of genital prolapse and it is very rarely necessary to combine it with a colporrhaphy if the colporrhaphy is properly performed. Very occasionally a patient has so little pelvic tissue that it is necessary to fix the uterus to the abdominal wall as well as to do an extensive colporrhaphy. I have found this combination necessary on only three occasions in the last seven years.

Treatment of retroflexion

In a large percentage of cases of genital prolapse the uterus is retroflexed. During the operation the uterus is replaced and usually remains in this position if the deep pelvic tissues are properly sutured. In some cases, however, the uterus will not remain in an anteфлекed position and some operators consider it necessary to secure this by the performance of an abdominal operation in addition to the colporrhaphy. If the operator regards retroflexion as a morbid condition which must always be rectified, he will often combine the operations. If, on the other hand, he holds the modern view that an uncomplicated retroflexion rarely produces symptoms, he will reserve this combined operation for a few cases in which he feels convinced that the retroflexion is producing symptoms quite apart from those due to the genital prolapse. In either event these are two separate operations, done for separate conditions, and the abdominal operation is not part of the cure of genital prolapse.

Hysterectomy

Hysterectomy is not a cure for prolapse and the most difficult case to cure is prolapse of the vaginal walls when the uterus has already been removed. A vaginal hysterectomy can be combined with a colporrhaphy (Mayo's operation), but these are two separate operations performed at the same time and the hysterectomy is for some condition of the uterus which requires its removal. In these cases special care must be taken in

suturing the pelvic floor, even more than when a colporrhaphy alone is performed.

The interposition operation is still performed in some schools, especially in America and on the Continent, where it is known by the name of Watkin, Schauter, or Wertheim. In this operation the bladder is separated from the uterus, the uterovesical pouch of peritoneum opened, and the body of the uterus brought through the opening and sutured to the vaginal muscle. It must never be performed on an unsterilized woman before the menopause and is therefore usually reserved for elderly women. As prolapse in old women can be cured by the less severe operation of colporrhaphy I have never seen a case in which an interposition operation was required. *Interposition*

In Le Fort's operation a longitudinal strip is dissected from both the anterior and posterior vaginal walls and when the edges of these are sutured the vagina is divided into two tubes with the uterus supported by the median raphe. In some schools this operation is still occasionally used for old women with poor pelvic tissue. *Le Fort's operation*

Colporrhaphy

Colporrhaphy is becoming more and more the universal method of treating all cases of genital prolapse. In some schools different operations are used for different circumstances, especially for patients of different ages. This is unnecessary as colporrhaphy will cure practically every patient, young or old, parous or nulliparous, provided she has any pelvic floor to be sutured. This does not mean that all colporrhaphies are alike: each one differs from the others according to the needs of the case. The incision may be wider in one and higher in another, and several layers of deep suturing may be necessary in another, and only experience can guide the operator. All, however, conform to one general principle, namely, rawing of the anterior and posterior vaginal walls with suturing of the deep pelvic tissues so as to strengthen and shorten the pelvic floor, and amputation of the cervix.

Colporrhaphy was first performed by Donald of Manchester in 1888 and has been used continuously in that centre from that date. Later it was somewhat modified by Fothergill and so is commonly known as the Donald-Fothergill or the Manchester operation. The following description of the operation follows in detail my own method which, in general principle, is that devised by Donald, modified in some details by Fothergill, and again by myself. *Donald-Fothergill operation*

Two complications are definite contra-indications to operation. Cystitis, even if the patient has almost recovered from the attack, will be lit up again and may lead to pyelitis. I have lost two patients in this way and now never operate in the presence of bladder infection. Ulceration of the cervix is common in procidentia. The ulcer is always septic and an operation in this stage is liable to be followed by serious sepsis in the wound. I have seen a fatal case and one of general pyaemia, and in the presence of this complication also I never operate. These ulcers will *Contra-indications*

always heal in three weeks or less if the patient will remain in bed, replace the cervix whenever it comes down, and douche twice daily, once with boric acid and once with alum, using one teaspoonful to the pint of warm water.

Preparation for operation

The vagina should be douched with an antiseptic lotion the day before the operation and the rectum emptied by an enema on the morning of the operation. When the patient is on the table the vagina and vulva should be swabbed with 70 per cent alcohol and 2.5 per cent solution of iodine in alcohol.

Technique

The patient is placed on the table in the lithotomy position, the vulva shaved, and this and the vagina are thoroughly cleansed with surgical spirit and solution of iodine. The cervix is then grasped with the volsellum and the canal dilated. Dilatation is necessary, as at a later stage sutures have to be inserted through the cervical mucosa. I always curette the uterus, to make quite sure that there is nothing abnormal in its interior.

The shortest and clearest method of description is to follow the illustrations. Fig. 36, *a* shows the method of stitching back the labia minora. A sterile towel with an opening somewhat larger than the vulva is placed over the patient, a weighted speculum inserted into the vagina, and a stitch inserted through the towel and subjacent skin of the buttock and then through the labium minus. When this is done on both sides, the labia are drawn well away from the vagina and so give a good view of the field of operation and present a smooth surface which is more easily sterilized. This illustration shows the left labium minus stitched to the buttock.

Fig. 36, *b* shows both labia minora stitched outwards. The cervix is grasped with a volsellum, pulled downward as far as possible and dilated, and the uterus curetted. A pair of Spencer Wells forceps grasps the vaginal mucosa on each side of the cervix, as far apart as it is judged necessary to make the base of the denuded area. This is a matter of experience and can only be judged correctly with practice. A triangular area is then marked out with the scalpel with its base near the cervix and its apex below the urethra, but the sides of the triangle are not quite straight as it is necessary to have the denuded area a little wider in the centre of the vagina than at the base. In a complete procidentia it is possible to mark out the whole triangle before separating any of the mucosa, but in cases of partial prolapse it is best first to mark out the lower portion and dissect this from the subjacent tissues; during this process the folds in the remaining portion of the vagina are smoothed out, and the outline of the triangle can be more easily completed. In practice, the base of the triangle is usually made somewhat wider than in this drawing.

Fig. 36, *c* shows the dissection of the vaginal mucosa from below upward. In a case of complete procidentia it is possible to begin the dissection from the urethra downwards, but in cases of partial prolapse it is much easier to begin at the base of the triangle near the cervix, and so I prefer to make this a routine practice in all cases.

Fig. 36, *d* shows the triangular area denuded of mucous membrane. The few fibres of muscle and connective tissue which fix the bladder to the cervix have been cut and this organ has been dissected up from the cervix. This exposes

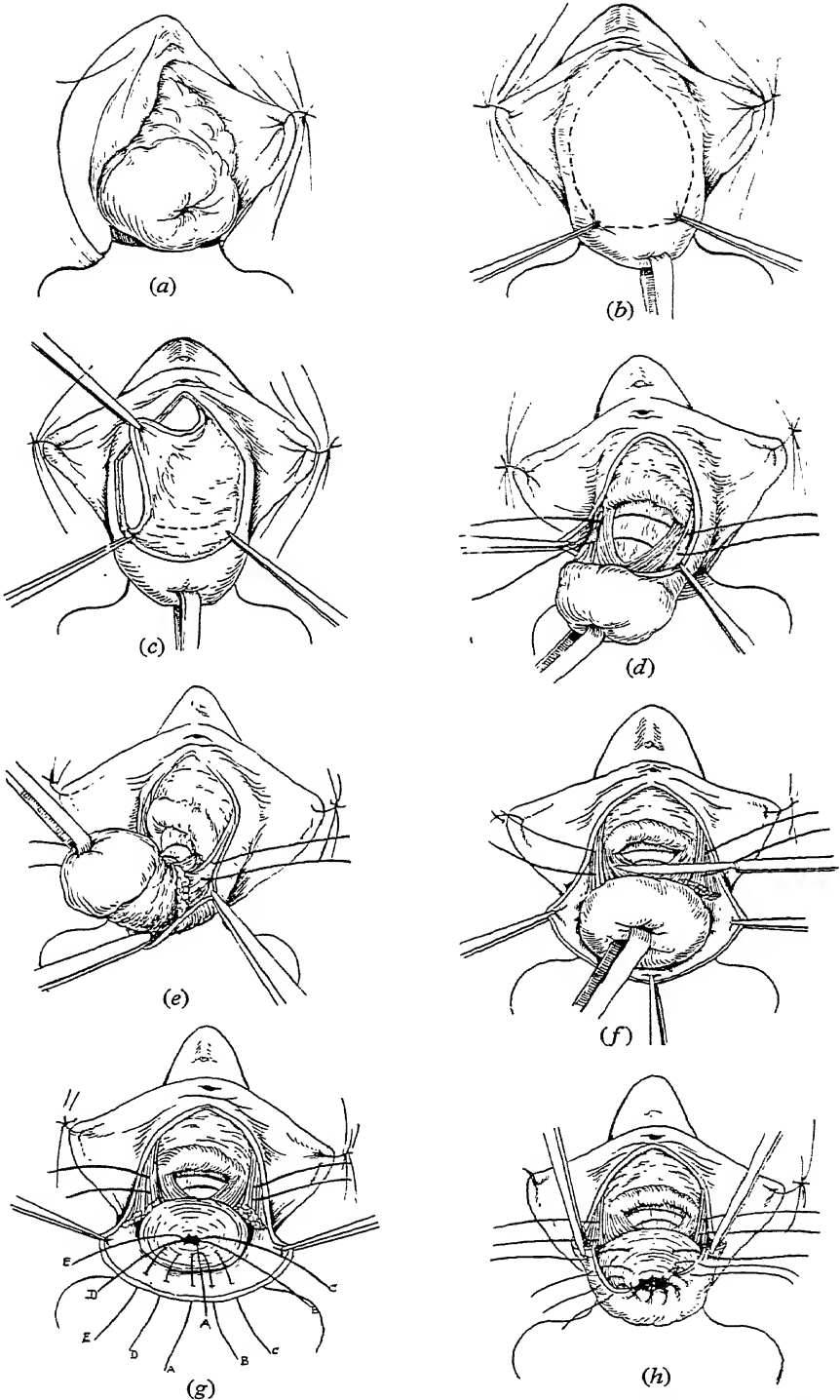


FIG. 36.—For explanation see text. (This and Figs. 37 and 38 from the *American Journal of Obstetrics and Gynecology*, 1933)

the muscular tissue and parametrium at the base of each broad ligament, and with a needle it is possible to encircle a mass of this tissue on each side. This sketch shows two sutures inserted, each of which includes a portion of this tissue on both sides. When these sutures are tied, this tissue from each side will be drawn to the front of the cervix, and therefore this portion of the pelvic floor will be shortened by this amount. The ligatures are not tied at this stage, but it is convenient to insert them while the tissues are visible. In most cases, the suturing of this material in front of the cervix is sufficient to keep the uterus anteфлекed, even though it was previously retroфлекed; but in a few cases in which the uterus is very heavy these sutures transfix a small portion of the anterior wall of the uterus and so keep this organ in the anteфлекed position while the healing process takes place.

Fig. 36, *e* shows the cervix drawn forward to show part of the posterior surface. An incision is made through the vaginal mucosa from one pair of Spencer Wells forceps round the back of the cervix to the pair of Spencer Wells forceps on the other side, and the mucosa is stripped from the cervix for a distance varying with the amount of cervix which requires amputation.

Fig. 36, *f* shows the cervix still grasped with the volsellum. The vaginal mucosa has been dissected from the cervix and the scalpel is shown in position, ready to amputate the denuded portion of the cervix.

In Fig. 36, *g* a portion of the cervix has been amputated. Sutures are now inserted through the cervix and the vaginal mucosa, and when these are tied the edge of the vaginal tissue will be brought into contact with the cervical mucosa.

Fig. 36, *h* shows a later stage with a few of the sutures tied. Finally a suture is passed through one angle of the mucosa, transfixes the centre of the anterior wall of the cervix, and lastly the other angle of the mucosa, and when these and a few intermediate sutures are tied the external os is completed.

Fig. 37, *a* shows the external os completed. Instead of a triangle, the denuded area is now oval, as the angles at the base have been brought together at the centre of the external os. By means of a continuous suture the cut edges of the mucosa are brought together up to the level of the insertion of the two deep sutures. At this stage the uterus should be examined, and if it is retroфлекed the body should be replaced. The two deep sutures which in Fig. 36, *d* are placed around the musculature at the base of each broad ligament are now tied, and if a ligature has been left on the cervix it will be found that no reasonable amount of traction will now pull the cervix down, as the deep sutures shortening and tightening this part of the pelvic floor prevent any further descent of this organ.

Fig. 37, *b* shows the two deep sutures tied and others inserted in the deep tissues at the base of the bladder. These additional sutures should always be inserted and are especially important in patients with incontinence of urine.

Fig. 37, *c* shows these deep sutures tied and a continuous suture inserted in the vaginal mucosa to complete the closure of the original incision.

Fig. 37, *d* shows the completion of this stage of the operation.

Fig. 37, *e* shows the method of marking out the flaps of the posterior colporrhaphy. The redundant tissue in the posterior fornix near the cervix is grasped by a pair of forceps, and when this is pulled forward the tissue falls roughly into a triangle, with its base on the perineum, but it is usually necessary to make the centre of the triangle as wide or almost as wide as the base, and this portion is marked out on each side by a pair of forceps, while the angle

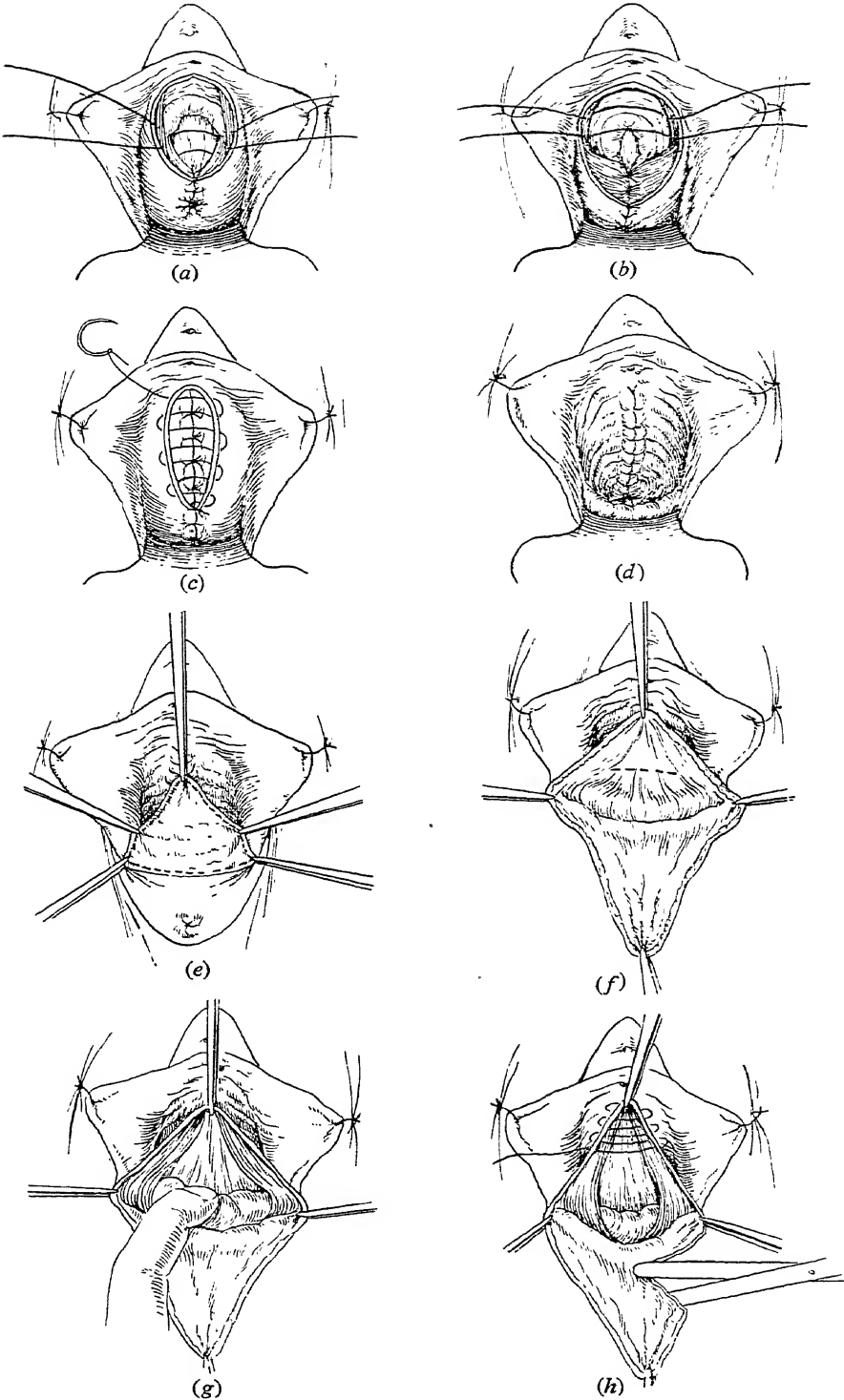


FIG. 37.—For explanation see text

on the perineum is marked on each side with another pair. In practice, it is easier to denude the triangle down to the middle forceps and to control bleeding by stitching these edges together before completing the triangle down to the perineum.

Fig. 37, *f* shows a triangle of vaginal mucosa dissected from the subjacent tissue. It also indicates the line of the rectum with some fine fibres of connective tissue attaching it to the vagina. The dots indicate the line through which these adhesions are incised.

In Fig. 37, *g* the attachments of the rectum have been cut and the rectum separated from the vaginal wall. This is the most important step in the operation, as without it it is impossible to fill in the space between the vagina and the rectum with muscle, and if this is not done the vaginal mucosa will stretch and will bring forward the rectum as a recurrent rectocele.

Fig. 37, *h* shows the continuous suture drawing together the upper edges of the triangle, and in practice this is usually completed before the remainder of the triangle is dissected away. This sketch shows the completion of this dissection with a pair of scissors cutting away the mucosa from the perineum. It also shows the rectum separated from the vagina, and on each side folds of muscular tissue which must be brought together by means of deep sutures. If the posterior colporrhaphy is carried sufficiently high the upper portion of this muscular tissue is part of the pelvic floor running at the base of the uterosacral ligaments and the tissue a little lower represents the levator ani muscles. The most important part of the posterior colporrhaphy is the suturing together of these deep layers of muscular tissue.

Fig. 38, *a* shows the upper portion of the edges of the triangle drawn together by a continuous suture, and also a few sutures inserted into the deep muscles. In the central area the rectum can still be seen but this space will now be closed by other deep sutures inserted into the muscle.

Fig. 38, *b* shows the completion of the suturing of the long sides of the triangle. The angles at the base of this triangle are brought together at what will be the centre of the new vulval outlet. As the vaginal edges are sutured, successive layers of deep muscle are folded together, and these are bound firmly together by means of deep sutures, usually in three different layers. In this sketch the vulval outlet is completed, one layer of sutures in the deep muscle is shown with the sutures tied and another layer inserted ready for tying.

In Fig. 38, *c* the edges of the skin on the perineum are brought together by a continuous subcuticular suture. The labia minora are still sutured to the buttock.

Fig. 38, *d* shows the completion of the operation. The sutures holding the labia minora have been cut and the edges of the skin of the perineum brought together.

Throughout the operation nothing but catgut is used as a suture material and so there are no stitches to be removed during convalescence. The most important part of the operation both in the anterior and the posterior colporrhaphy is the suturing of the deep muscle, as this shortens and strengthens the whole of the pelvic floor, the tissue which alone keeps the uterus in position. The excision of the vaginal mucosa merely removes tissue which otherwise would be redundant and gives access to the deep musculature, and the suturing of this vaginal mucosa is done only with a continuous suture and merely to promote quick healing and to control the oozing. This tissue itself is of no value in keeping the uterus in position, and if the pelvic musculature is not firmly sutured the prolapse of the uterus will quickly recur.

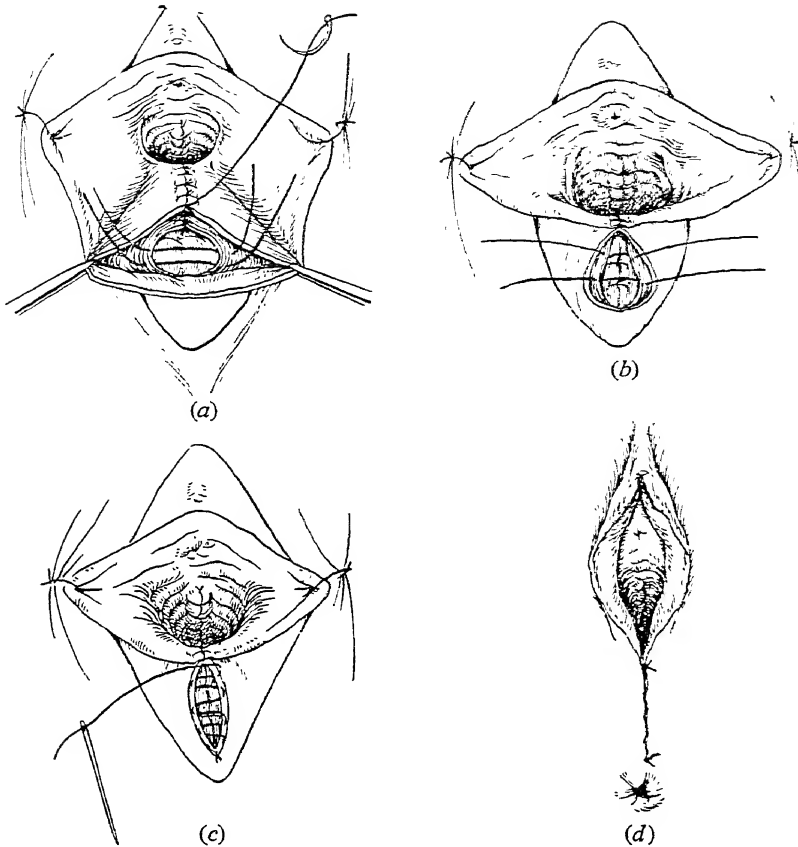


FIG. 38.—For explanation see text

After-treatment and treatment of complications

There should be as little interference as possible with the operation site. At the end of the operation the vagina is lightly packed with gauze dipped in bismuth, iodoform, and paraffin paste; this limits oozing and keeps the vaginal walls separated and the B.I.P.P. prevents the gauze from damaging the vaginal tissue. The gauze is removed in twenty-four hours. A sterile dry pad is kept over the perineum, which is kept as dry as possible during the healing process. After micturition and defaecation the parts are gently swabbed with surgical spirit to keep them clean and dry. The bowels should be moved on the third day, liquid paraffin and liquid extract of cascara sagrada being the aperient generally used as it gives a soft motion. If the perineum is healed the patient can get up at the end of a fortnight, but in many cases a few days longer are required. Most important of all, the patient must avoid any strain on the pelvic muscles for three months as the tissues can be stretched during this time. During this period she must not stand for long, play games, or increase intra-abdominal pressure by use of her abdominal muscles.

Retention of urine often follows the operation; the patient should be

Retention of urine encouraged to pass urine but in a number of cases catheterization will be required and there is always a risk of resulting cystitis; a self-retaining catheter does not diminish the risk of infection. An intramuscular injection of doryl often produces spontaneous urination.

Haemorrhage Haemorrhage about one week after the operation occasionally occurs, due to incomplete healing of the cervix when the sutures give way. This usually means a slight degree of sepsis and the best treatment is to give an antiseptic douche such as diluted dettol and to insert an iodox pessary. This should be repeated for four or five consecutive days and, if it is begun at the first signs of a pink discharge, it is rarely necessary to do anything further. Very occasionally it is necessary to pack the vagina with gauze or even to insert a suture.

Results of treatment

The results of the operation of double colporrhaphy with amputation of the cervix are so good that in more and more centres it is becoming the only method of treatment. No operation for any condition can give one hundred per cent of cure, but this one nearly approaches this ideal. Some years ago, in order to assess the value of the operation, I wrote to a large number of consecutive patients who had been operated upon more than three years previously and received replies from 664. Of these only 24, or 3·61 per cent, were not completely satisfactory. But even this is much too high a figure as five of these had subsequently had children and 5 failed to come for examination. Of the 24 cases only 5, or 0·75 per cent, had any condition which justified further operative procedure and these were all cured by a second operation.

Mortality The operation takes about half an hour to perform and does not impose any great strain upon the patient, certainly much less than any abdominal operation. The mortality is very low, in 2,152 cases only 0·37 per cent.

Effect on incontinence of urine Incontinence of urine is a little more difficult to cure than the other symptoms as the muscular tissue stitched over the urethra sometimes stretches. In these cases it is necessary to carry the anterior colporrhaphy forward, almost to the urethral orifice, and to plicate two and if possible three layers of muscular and connective tissue over the urethra. This is usually successful, provided that the patient will take much rest and not subject the parts to strain for three months.

Results in elderly patients In elderly and old women the results are particularly good. This series included 5 patients aged respectively 70, 70, 71, 73, and 75 years, all of whom were cured. The one of 73 years of age reports that she does all her own work and can walk for miles.

Results in nulliparae Genital prolapse in nulliparae is not very common but in Lancashire a few examples are seen every year, because so many women do hard work in the cotton mills. As there must be some developmental weakness of the pelvic floor it might be expected that the results of this operation, which depends upon the strengthening of this structure, would be bad. This is not so, as in my last 32 cases 31 were completely cured.

These included two virgins of 16 years of age and three of 63 years of age. One virgin, now over sixty years of age, reports that she is a weaver and does a full day's work looking after three looms.

Subsequent parturition

When a patient is advised to have this operation, knowing that the condition was produced in the first place by parturition, she is likely to ask: 'Will it recur if I have other children?' As the operation as nearly as possible replaces the pelvic floor into its original position there must always be a risk of recurrence of the prolapse with subsequent confinements. There is therefore a tendency to defer this operation until the family is completed. With due care during parturition, however, this recurrence is by no means inevitable and in 30 of my patients who subsequently had children 5, or 16·5 per cent only, had any signs of recurrence; in no instance was the labour more difficult and in some it was made easier, in all probability as a result of removal of part of the cervix. The practical application of this is to defer operation until after the completion of the family if the patient can be made comfortable with a pessary. If, however, the patient is not comfortable or dislikes the necessary cleansing and replacement of this instrument, a colporrhaphy can be done with the knowledge that subsequent confinements will not be more difficult, but that the patient must take a 20 per cent risk of recurrence of the prolapse, which again will require a colporrhaphy for its cure.

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IV.—TUMOURS

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1.—CLASSIFICATION

1586.] The uterus is particularly liable to the development of both benign and malignant new growths. The 'tumour types' which affect the organ may be classified as follows. (i) Benign: (a) connective-tissue tumours: fibromyoma and lipomyoma; (b) epithelial tumours: adenoma and adeno-fibroma (polypi); and (c) combined epithelial and connective-tissue tumours: adenomyoma (endometriosis). (ii) Malignant: (a) connective-tissue tumours: sarcoma, endothelioma, and perithelioma; and (b) epithelial tumours: carcinoma and chorionepithelioma.

Adenomyoma (*synonyms*: endometrioma, endometriosis), adeno-fibroma including uterine polypi, and chorionepithelioma (*synonym*: deciduoma malignum) are described in the articles ENDOMETRIOSIS AND ADENOMYOMA, Vol. IV, p. 561; and CHORIONEPITHELIOMA AND HYDATIDIFORM MOLE, Vol. III, p. 220.

2.—FIBROID TUMOURS

(1)—Definition

(*Synonyms*.—Fibromyoma; fibroma; myoma; leiomyoma; fibroid)

Fibroid tumours of the uterus are benign new growths composed of white fibrous tissue and plain muscle in varying proportions. The smallest growths are essentially myomas, being composed entirely of muscle elements.

(2)—Aetiology

The causation of uterine fibroids, probably the commonest tumours occurring in the human species, is unknown. That these tumours never develop before puberty or after the menopause suggests that their growth may be a response to the tissue-stimulating properties of a sex hormone or to the local periodic vascularity of the uterus engendered by such. The influence of race, heredity, and sterility have

all been noted as possible aetiological factors in support of the view that an initial focus is laid down in the course of development and during foetal existence. The greater incidence of fibroids in black than in white races is established. From post-mortem records the incidence amongst white races is as high as one in four or five women. Thus Lockyer in 150 consecutive necropsies found myomas present in 30. Among negroes the incidence is still higher. An occasional example may be encountered between twenty and thirty or even before twenty, but the years thirty-five to forty-five provide by far the greater number. These are the years during which myomas are most likely to come under observation because of the symptoms which they produce. Heredity as a factor in aetiology is perhaps more debatable, but there is no doubt that certain families exhibit a marked tendency to develop new growths of this type.

Heredity

Sterility

The association of fibroids with sterility is also commonly accepted (30 per cent as against an average sterility rate of 10 per cent), but the relation between the two can only be a matter of conjecture. A sterile woman does not necessarily grow fibroids in her uterus, neither is a woman with a fibroid uterus always sterile, but sterility appears to predispose to these new growths. Opinion differs as to the higher incidence of these tumours in the married and the unmarried. The assertion that all elderly virgins are subjects of myomas is an exaggeration.

Inflammatory lesions

Inflammatory diseases of the Fallopian tubes are commonly associated with uterine fibroids. In a series of 3,561 cases collated by Tracey, inflammatory lesions in the Fallopian tubes co-existed in 14.5 per cent. The conditions essential for the development of fibroid tumours in the uterus, why they are single or multiple, and what predestines the site of growth in the individual organ, remain problems of gynaecological pathology at present unsolved.

(3)—Morbidity Anatomy

(a) *Histological Classification*

Origin

'Seedling fibroids'

Capsule

All fibroid tumours of the uterus are primarily interstitial in position, i.e. they develop in the muscle of the uterine wall. Whether they originate from the adventitia and media of vessel walls or by a process of metaplasia from the muscle fibres of the uterus is undecided. The smallest growths, commonly termed 'seedling fibroids', are composed only of spindle-shaped muscle-cells containing long nuclei rounded at their ends. At this early stage no separate capsule can be recognized, but the closely packed cells with well stained nuclei distinguish the developing new growth from surrounding normal uterine tissue. As the tumour grows, a peripheral lymphatic cleft appears between it and the adjacent tissues, and emphasizes the encapsulated and benign character of the new growth even before the true capsule has developed. 'Seedling' fibroids may be quite unrecognizable to the naked eye or touch, a fact which has some bearing upon the operation of

myomectomy, inasmuch as this conservative therapeutic method can never guarantee the eradication of all new growths that may be present.

Any part of the uterus may be the starting point for a fibroid. The majority develop in the body of the organ, the cervix uteri being the seat of election in but 8 per cent of cases. Very rarely the uterine ligaments, e.g. the round or the ovarian, are primarily involved. These tumours are generally multiple, the incidence of the single tumour being only 1 or 2 per cent. Although in the first instance intramural in position, many myomas in the course of their growth approach either the peritoneal or the endometrial surfaces of the uterus. This has resulted in the common classification of these tumours into 'interstitial', 'subperitoneal', and 'submucous' types. The classification is useful in that each group is associated with definite clinical features. A fibromyoma may also undergo various changes by virtue of its anatomical relation to the uterine wall.

Site

*Classification
by site of
origin*

Interstitial fibroids

Interstitial fibroids of the uterus appear as hard, rounded, or oval tumours which, because of the loose connective-tissue capsule sur-

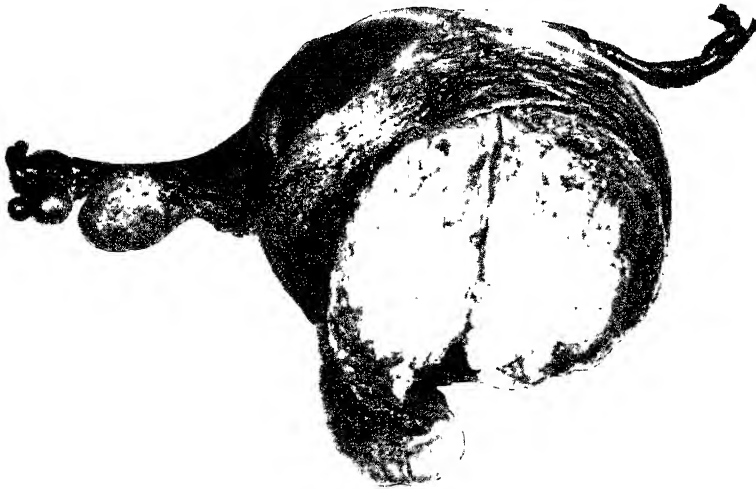


FIG. 39.—Single interstitial fibroid of posterior uterine wall showing the white whorled appearance of an uncomplicated tumour

rounding them, can readily be enucleated from their bed. On section, small or moderately-sized growths present a white appearance, the surface being roughly lobulated as the result of interlacing fibres.

The capsule which surrounds an interstitial fibroid and which sharply demarcates the tumour and surrounding healthy uterine tissue consists largely of muscle fibres. When one of these growths is enucleated the capsule contracts and retracts together with the uterine wall, a fact of considerable importance in limiting the amount of haemorrhage during surgical removal. The muscular and fibrous tissue

Capsule

of the capsule is arranged loosely in parallel bundles in contradistinction to the dense interlacing fibres which constitute the tumour. The capsule also contains a liberal vascular and lymphatic supply. Blood-vessels in the tumour are few in number and small in size, except in rare instances termed 'telangiectatic fibroids' (Virchow).

Single large fibroids are generally of the interstitial type. In such cases the growth produces considerable enlargement of the uterus, and the length of the cavity may be increased to four or five inches



FIG. 40.—Large single interstitial fibroid of posterior uterine wall showing elongation of uterine cavity and polypoid hyperplasia of endometrium

*Hyperplasia
of uterine
muscle*

or even more (see Fig. 40). The development of an interstitial fibroid in the wall of the uterus results not uncommonly in considerable hyperplasia of the uterine muscle, so that after enucleation of the tumour the organ may still be twice its normal size. This hyperplasia is probably caused by increased vascularity associated with the presence of a large interstitial growth. Interstitial tumours are commonly associated with subperitoneal and submucous growths, the whole forming a tumour mass which in some cases leads to great distortion of the uterus and may reach immense dimensions; growths weighing 47, 89, and even 180 lb. are on record.

Subperitoneal fibroids

Subperitoneal, or subserous, fibroids result from the gradual growth of interstitial myomas towards the serous surface of the uterus. The tumour first appears as a small rounded prominence on the surface.

At this stage, when the new growth is sessile and appears to the naked eye to be lying immediately below the peritoneal coat of the uterus, a small covering of muscle may be demonstrated microscopically: i.e. the fibroid is still strictly interstitial. Finally the tumour is extruded from the uterine wall, to which it remains attached by a stalk or pedicle of varying thickness.

The pedicle contains muscular tissue and conveys blood-vessels and lymphatics which, in large tumours, are of considerable size; in subserous uterine fibroids it is usually flat and broad. Although considerable mobility of the tumour is possible, torsion of the pedicle is rare in comparison with the frequency of this accident with ovarian tumours. Growths of moderate size with much elongated peritoneal stalks, however, occasionally do undergo an acute twist and in some cases become completely detached from the uterus. Such a tumour may acquire secondary attachment to, and be vascularized by, the omentum and is then called a 'parasitic fibroid'.

*Pedicle**Torsion**'Parasitic fibroid'*

Pedunculated subperitoneal fibroids may reach an immense size and are some of the largest abdominal tumours known. Owing to their free mobility they soon rise into the abdominal cavity, but a subperitoneal tumour growing from the posterior wall of the uterus easily becomes incarcerated in the recto-uterine fossa (pouch of Douglas) below the sacral promontory. Owing to deficient blood-supply, subserous fibromyomas commonly undergo various types of degeneration, hyaline and cystic change being perhaps the most common. The uterus, even when associated with multiple, and in some cases very large, subperitoneal fibroids, is by no means always increased in size. Indeed it may be possible to remove a number of large growths of this type and to leave an organ comparatively normal in shape and dimensions. A subperitoneal pedunculated fibroid therefore presents a very different proposition from a large single interstitial tumour of similar size, both in symptoms and treatment.

*Size**Degeneration*

Subserous tumours developing from the lateral wall of the uterus separate the folds of the corresponding broad ligament and are then known as intra-ligamentary. Such tumours, and also those which grow from the anterior or posterior walls of the uterus below the peritoneal reflexion, displace the organ and, since they cannot rise into the abdominal cavity, are particularly liable to cause severe pressure symptoms. When retroperitoneal fibroids find their way into the general abdominal cavity they cause much displacement of adjacent viscera. Large tumours may extend in the cellular tissue of the abdominal wall as high as the lower pole of the kidney, and displace the caecum or pelvic colon forwards according to the side of the abdomen which they affect.

Intra-ligamentary tumours

Cervical fibroids

A cervical fibroid may be regarded as a type of retroperitoneal growth. The supravaginal portion is usually affected, fibroids of

*True cervical
fibroids*

*'False'
cervical
fibroids*

the vaginal portion of the cervix being very rare. Cervical myomas are generally single and appear to be associated more commonly with the posterior than the anterior wall. Two types must be distinguished, the 'true' and the 'false'. A true cervical fibroid develops within the tissues of the supravaginal cervix, and the cervical canal is always much elongated. The body of the uterus is of normal size and pushed upwards by the growth of the rounded or oval tumour which occupies the pelvic cavity; it can often be palpated above the pubes. 'False' or 'pseudo'-cervical fibroids are attached to the supravaginal cervix by either a pedicle or a broad base. They develop in a retroperitoneal position and cause considerable dislocation of adjacent structures such as the ureters and the uterine vessels. These facts should be remembered when such tumours are being surgically removed.

Submucous fibroids

Submucous fibroids, like the subserous types, are generally considered to arise from the development of an interstitial tumour towards the



FIG. 41.—Large submucous fibroid of 'cup and ball' type: the single tumour completely fills the dilated uterine cavity

Fibroid polyp

endometrium lining the uterine cavity. A 'seedling' microscopical myoma, however, occasionally grows in such close relation to the endometrium as to be submucous *ab initio*. Submucous myomas are often single, in which event they may be sessile with a broad base or be pedunculated. As a result of periodical uterine contraction a submucous tumour tends to become pedunculated and polypoid early. The stalk may be so lengthened as to allow the tumour to be extruded through the cervical canal and occasionally even outside the vulva. During the process of expulsion of a pedunculated submucous fibroid from the uterine cavity, uterine polarity results in the cervix being widely dilated.

Large submucous tumours on the other hand always maintain a broad base of attachment to the uterus. The cavity of the organ then increases in size and the tumour is moulded to the contour of the uterine wall. A large fibroid may be partly interstitial and partly submucous. The uterus enlarges symmetrically and the fibroid distends the cavity in a 'cup and ball' manner (see Fig. 41).

Occasionally submucous fibroids may be small and numerous, filling the cavity of the organ like calculi in the gall-bladder. The analogy is *Multiple submucous fibroids*



FIG. 42.—Multiple small submucous fibroids showing 'faceting' caused by close apposition of tumour surfaces: at \times a 'seedling' fibroid in an 'interstitial' position is seen

rendered closer by the faceted appearance of some of the small tumours (see Fig. 42). A submucous fibroid in process of expulsion may cause spontaneous inversion of the uterus; this, however, should always arouse the suspicion of possible coexistent malignancy of a sarcomatous nature, since the normal healthy uterine fundus does not readily undergo inversion. *Inversion of uterus*

The tumour is at first covered completely by endometrium, but with increased growth the tissue at the distal pole becomes more and more attenuated until it is represented by a single layer of cells. In the recesses and angles at the base of the fibroid, and often over the rest of the uterus, the endometrium is commonly hypertrophic or polypoid (see Fig. 40). *Endometrium*

Metaplasia

During menstruation this hyperplasic endometrium is congested either diffusely or locally, and it is from this surface, as distinct from the tumour, that the severe bleeding associated with submucous fibroids occurs. When a pedunculated submucous fibroid occupies the vagina the covering endometrium commonly undergoes metaplasia to a squamous type of epithelium. Owing to defective vascular supply and exposure, such tumours not uncommonly become inflamed or necrotic. Rarely the interstitial or subperitoneal forms are so affected.

Although the majority of submucous fibroids are of moderate size or small when they first come under observation, a tumour in this position may reach dimensions comparable to those of a twenty-four weeks' gestation. The enlarged uterus is then of uniform shape and consistence and may simulate the pregnant organ.

*(b) Morbid Changes in Fibroids**Malignant metaplasia*

Fibromatous tumours of the uterus often show secondary morbid lesions, mostly associated with alterations in the vascular supply, a deficiency resulting in various degenerative changes, e.g. hyaline, cystic, fatty, calcareous, or necrobiotic. Impaction or incarceration of a fibroid is soon followed by oedema and lymphangiectasis. Axial rotation of a subperitoneal pedunculated tumour is associated with congestion and haemorrhage, or necrosis of the growth. A tumour may also become inflamed as the result of infection from the endometrium or directly from a coil of adherent intestine. If the infection is sufficiently acute, gangrene and sloughing occur. Suppuration within a fibroid, however, is rare. Finally, malignant metaplasia of a mesoblastic type converting the originally benign new growth into a highly malignant sarcoma occurs in slightly under 1 per cent of observed tumours.

*Hyaline degeneration**Naked-eye appearances**Microscopical appearances*

Hyaline degeneration is very common in all types and is the usual concomitant of malnutrition from vascular deficiency. To the naked eye such a tumour on section shows dull grey areas contrasted with the white appearance of the healthy tumour. Under the microscope it will be seen that irregular areas of fibrous tissue are replaced by a homogeneous material which stains readily with eosin and fuchsin. The muscle elements are usually intact and even in advanced cases the nuclei of the muscle-cells retain the haematoxylin stain. The same resistance is shown by the vessel walls. The distribution of hyalin in a fibroid tumour varies within wide limits. Sometimes only a small area is affected; in other cases the whole growth may be involved in either a trabecular or patchy manner. Lockyer drew attention to the close association between hyaline degeneration in a fibromyoma and sarcomatous metaplasia of the muscle-cells.

*Association with sarcomatous metaplasia**Cystic degeneration*

Cystic degeneration is generally the result of liquefaction of hyaline areas, the distribution of these areas determining the size, shape, and

character of the cystic spaces. The latter are lined by hyaline tissue and in no sense are they true cysts. In most instances cystic degeneration affects a tumour in a honeycomb manner producing a congeries of small spaces containing albuminous straw-coloured fluid. Occasionally large cavities are formed by the liquefaction of corresponding plaques of hyaline tissue, or by the absorption of trabeculae between adjacent cysts. Rarely liquefaction is so extensive as to involve nearly the whole of a tumour, converting it into a single large cyst. Admixture of the contained fluid with blood pigment results in a brown or reddish-brown appearance of the contents. Cystic degeneration is also occasionally associated with a 'necrobiotic' fibroid (see below), when the contained fluid is dark red and resembles venous blood.

*Naked-eye
appearances*

True cysts, i.e. spaces lined by epithelium or endothelium as distinct from cystic degeneration, are rare in fibroid tumours of the uterus. When they occur they are probably the result of dilatation of lymphatic channels (lymphangiectasis) or of included uterine glands. In the latter instance the tumour is probably an adenomyoma (see Vol. IV, p. 561) and not a true fibromyoma.

True cysts

Fatty degeneration

Fatty degeneration affects the myomatous elements of a fibroid and is preceded by hyaline change. Fresh sections, appropriately stained, show fat-droplets in the line of the muscular fibres. The cause of this degeneration is probably a vascular defect, e.g. local thrombosis, but the precise determining factor is unknown. Not uncommonly one tumour among a large number is affected, when it may be homogeneous in appearance without the typical 'whorled' appearance of the unaffected fibroid (see Fig. 39). The colour is cream or yellow but varies according as haemolysis has or has not taken place. In such an event the transition to necrobiotic degeneration is very close. Fatty degeneration always precedes the deposition of calcareous salts and is more likely to occur in elderly subjects.

Cause

Calcification

Calcareous fibroids are the result of deposition in the tissues of calcium carbonate and calcium phosphate. This deposit may be scattered homogeneously throughout the growth or form a shell at the periphery. All types of fibromyoma are liable to this change which is more common after the menopause; it is always preceded by hyaline and fatty degeneration. Soaps and soap-albumins are formed and unite with calcium derived from the blood. Calcification in a myoma can be detected by radiography. Calcified tumours of this type (womb-stones) have been found in the pelves of female Egyptian mummies.

Necrobiotic degeneration

Necrobiotic degeneration, although not the commonest, is perhaps the most interesting morbid change. Fibroids which have undergone

this degeneration are comparatively soft and vary in colour from yellow or grey to deep red. The more extreme examples resemble uncooked meat, and the alternative names of 'raw-beef' or 'red' degeneration are sometimes applied. Necrobiotic fibroids can hardly be classed as a morbid entity since the morbid change is not specific. They are extreme types of necrosis with associated fatty degeneration and extensive staining with blood pigment. The use of these terms has become restricted partly as the result of the striking naked-eye appearance (see Plate XI, A), and partly from the clinical association with pregnancy, although co-existing pregnancy is not an essential requirement. The large, single, intramural fibroid is most commonly affected. Occasionally necrobiosis is seen in one tumour only, even when many are present.

Incidence

A pedunculated subperitoneal fibroid may be the seat of necrosis with haemolysis. It is seen not uncommonly in association with calcareous degeneration of the peripheral vessels in elderly patients. The term necrobiosis is perhaps a misnomer, but its continued use is justified because there is clinical evidence to show that some of these fibroids recover, and because the tissue is not dead as the word 'necrosis' implies. A tumour in which red degeneration is well established is tender and often associated with slight pyrexia. In some cases in which surgical intervention has been withheld, during pregnancy for example, these symptoms have subsequently subsided.

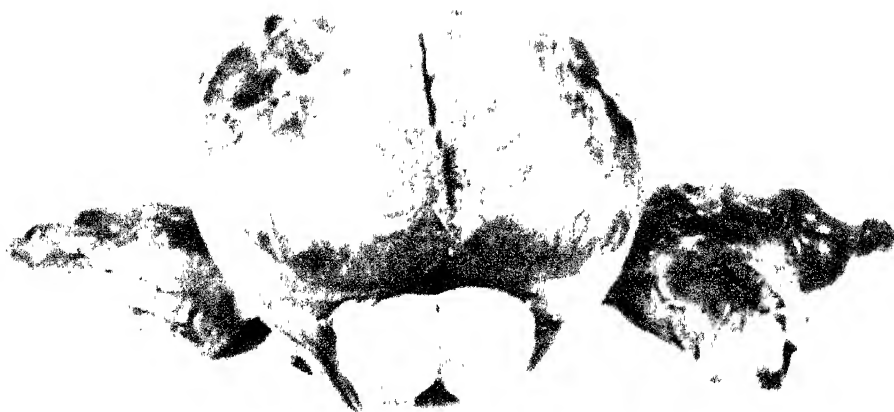
Symptoms

*Naked-eye
appearances*

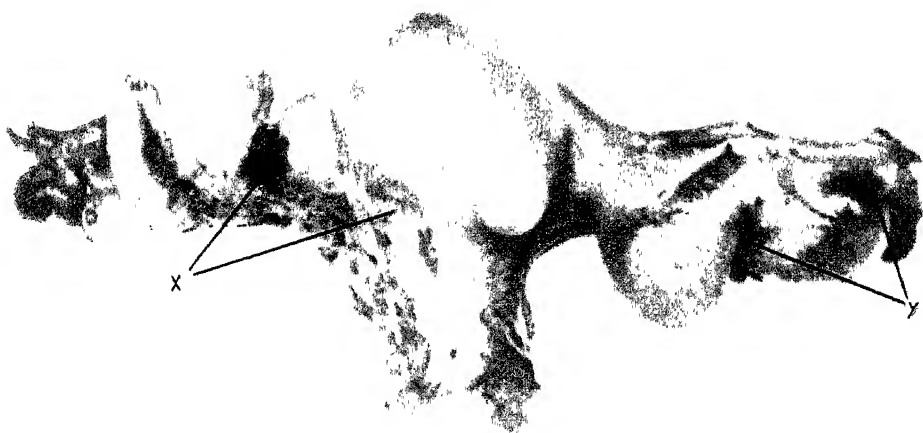
On section a necrobiotic fibroid presents definite characters. Apart from the unusual colour and consistence, the presence of thrombosed vessels in the capsule should be noted. An additional feature is the unpleasant odour described as 'musty', 'fishy', 'mousy', or resembling acetamide. The special features of this type of degeneration have no relation to inflammation or infection. Bacteria have been noted by some observers, but it is now generally accepted that the bacterial infection is secondary and of no aetiological importance.

Atrophy

Atrophy, in association with uterine fibroids, is of no great significance, especially from the clinical standpoint. The opinion is held by some practitioners and by many others that at the menopause fibromyomas not only atrophy but may disappear. It is true that with the cessation of ovarian function some tumours of this type become smaller, but the possibility of this happening should never influence the course of treatment which the immediate symptoms otherwise indicate. I have no personal experience of the total disappearance of fibroids by atrophy, and am sceptical about its occurrence. Lawson Tait in 1882 removed ovaries with the purpose of producing atrophy in fibroids, and the same principle is now applied in some clinics by irradiation with X-rays. Cross-fire application produces a primary atrophy of the ovaries, and this may result in subsequent atrophy of the uterus and any fibroids it contains.



A



B

- A. Interstitial fibroid undergoing early necrobiotic degeneration, or necrosis with haemolysis.
 B. Fibroid and endometriosis of the ovaries. Both ovaries are the seat of 'endometriomatous foci' which are shown at X and Y. The left ovary was densely adherent to the posterior wall of the uterus at the points indicated (X)

PLATE XI

Oedema

Oedema in a fibroid is caused by partial obstruction of the lymphatic vessels. It is the result of mechanical compression, as when a tumour is incarcerated within the pelvic cavity, and is therefore an uncommon complication. Such a tumour is soft and on section exudes much serum with a low albumin content, thus differing from the highly albuminous exudate associated with the liquefaction of hyaline areas. Care must be taken not to confuse a fibroid which is the seat of extensive cystic degeneration with this lesion. Both tumours exude much fluid on section, but the morbid anatomy of each is entirely different. When the lymphatic channels are much dilated lymphangiectasis results.

Torsion

Axial rotation of a pedunculated subserous fibroid is uncommon. Partial torsion causes extreme congestion of the tumour with interstitial haemorrhages into its substance. Such fibroids are purplish-red and usually adherent to neighbouring structures, e.g. omentum or a loop of intestine. Reference has already been made to 'parasitic fibroids' (see p. 453). Very rarely, complete axial rotation of the uterus occurs together with a fibroid. Bastianelli recorded an instance of such acute torsion that the uterus was amputated at the level of the internal os.

*With axial
rotation of
uterus*

Inflammation

Inflammation of fibroid tumours is limited almost entirely to submucous types, the reason being that the infection is usually ascending and conveyed via the endometrium. Occasionally infection of a myoma occurs directly through the intestinal wall or even through the bloodstream. Co-existing pelvic peritonitis (perimetritis), salpingo-ovaritis, or pelvic endometriosis are usually associated with wide-spread adhesions, often very dense, over the surface of a fibroid.

*Mode of
infection*

Sloughing

Invasion of a fibroid by saprophytic organisms results in gangrene or sloughing. Exposure of the growth to the infecting organism is essential, and therefore sloughing occurs in the submucous tumour, especially when polypoid and occupying the vaginal canal. A common cause of sloughing is trauma to the capsule, either by instrumentation, e.g. curettage, or by spontaneous tearing during extrusion of the tumour from the uterus. Sloughing fibroids are always associated with a most offensive discharge related to the tissue products of bacterial activity.

Malignant metaplasia

Uterine fibromas may be invaded either by a carcinoma or sarcoma from adjacent organs, or by a malignant new growth which has developed independently in the uterus. On the other hand sarcoma may appear *de novo* in a fibroid, as the result of metaplasia of either the fibrous or myomatous elements. Perithelioma and endothelioma may also arise from the blood-vessels or capillaries of a benign new

Invasion

*Metaplasia
of tumour*

Incidence growth. The incidence of sarcomatous metaplasia is variously quoted as between 1·21 (Cullen) and 1·5 per cent (Tracey); these figures appear rather high, and probably 1 per cent is more nearly correct. Microscopically, sarcomas derived from connective tissues are either spindle-celled or round-celled, those of muscle origin being spindle-celled. It is not easy always to recognize the spindle sarcomatous cell in a fibromyoma, and histological mistakes occasionally happen. The typical malignant cell is large and has a large nucleus with mitotic figures. The cell tends to become angular and to develop branching processes. Extraordinary examples do not show any of these criteria but metastasize in spite of the microscopical innocence of the primary uterine growth. Such tumours have been termed 'malignant leiomyomas'.

Malignant leiomyomas

Naked-eye appearances To the naked eye, a fibromyoma undergoing extensive sarcomatous metaplasia presents a characteristic appearance. In consistence the affected area is softer than the usual fibroid, its colour is creamy or yellow instead of white, and the typical whorled appearance of the cut section is absent. The degenerated growth contains areas of blood-stained tissue or even cysts containing blood-stained fluid, the distinction between malignant and non-malignant areas being usually well defined. The central area of a fibromyoma is most commonly the first to be affected by malignant metaplasia. The close association of hyaline degeneration with sarcomatous metaplasia of adjacent myomatous cells has already been noted.

(4)—Clinical Picture

Effect on fertility and menopause How long a tumour may exist before it causes symptoms is not known, this factor depending on the position of the fibroma in the uterine wall, its vascularity, and its rate of growth. In many cases, especially with subperitoneal fibroids, the size of the tumour first brings the patient under observation. Amazing instances sometimes occur in which an immense fibroid is present without apparently causing any symptoms and is not noticed by the unobservant woman. The association of fibroids with sterility has already been noted (see p. 450). Among women with fibroids the menopause is commonly delayed, and it is not uncommon to find such women menstruating at the age of fifty-five or more.

Primary and secondary symptoms The symptoms may conveniently be classified as primary and secondary; the primary group includes haemorrhage, leucorrhoea, pain, pressure effects, and sterility. The secondary group contains such clinical phenomena as anaemia, dyspepsia, constipation, and asthenia.

Haemorrhage

Factors determining haemorrhage Haemorrhage is probably the most usual symptom but excessive bleeding from the uterus is by no means constant or essential. Its incidence depends upon two and possibly three factors, namely: (i) the position of the fibroid in the uterus, (ii) the secondary effects induced

in the uterus and particularly in the endometrium, and (iii) coincident lesions in the ovaries resulting from associated circulatory changes in the pelvic organs.

In subperitoneal tumours the uterus may be normal in size and its endometrium unaltered, the menstrual function being little, if at all, affected. Bleeding is most in evidence with submucous growths, particularly when polypoid and in process of extrusion from the uterine cavity. In such circumstances repeated severe and finally continuous haemorrhage soon establishes profound secondary anaemia. *Subperitoneal fibroids*

Interstitial fibroids may or may not be associated with excessive or prolonged uterine bleeding. In most instances the uterine cavity is not only increased in size but is distorted and the endometrium hypertrophic or polypoid, and under these conditions haemorrhage is always excessive. At first the period may simply be increased in amount (menorrhagia); later it becomes prolonged (menostaxis), until finally one function merges gradually into the next. Menstrual irregularity usually implies secondary changes in the ovaries in the form of oedematous Graafian follicles which fail to mature or luteinize. *Interstitial fibroids*

Haemorrhage from a fibroid uterus is rarely immediately fatal, but death is not unknown. The secondary anaemia following repeated haemorrhages over a long period may, however, be severe and, since other symptoms may be absent, a woman at the menopausal age may pass into a dangerous state of asthenia before advice is sought. Haemorrhage is serious when a patient complains that she feels weak and listless at the close of the menstrual period or that it takes her a week or ten days to recover. *Anaemia*

Leucorrhoea

Many patients with fibroids notice an increase in the normal vaginal discharge, which in some cases is not only a source of discomfort by reason of its excess but also irritating and a cause of vulval pruritus. Endometrial hypertrophy, especially when polypoidal, accounts in most cases for troublesome leucorrhoea of this type. Occasionally it may be associated with co-existing catarrh of the cervical mucosa (endocervicitis) or with a cervical erosion (see also Vol. VII, p. 715). When a submucous fibroid is sloughing and infected with saprophytic organisms, a profuse and most offensive discharge, which may or may not be mixed with blood, is always present. *Pruritus*

Pain

Pain is not a common symptom of myomas. Ordinary simple fibroids are not painful, and pain usually signifies some secondary change or an associated pelvic lesion, not necessarily related to the tumour. Necrobiosis may render a fibroid painful and tender, as may the onset of malignant metaplasia, the pain increasing with extension of the sarcomatous growth. An inflamed fibroid is painful, but the cause of the inflammation is generally outside the tumour, e.g. an adherent pyosalpinx or inflamed pelvic appendix, and it is the associated lesion *Complications causing pain*

*Pain in
uncomplicated
fibroids*

which produces the local discomfort. But infection of a submucous tumour and sloughing may cause severe pelvic pain and pyrexia. Among cases of fibroids in which pain is the symptom to bring the patient under observation, it is not unusual to find an associated pelvic endometriosis (see Plate XI, B). Keene and Kimbrough in a series of 118 cases of endometriosis found uterine fibroids in 55.4 per cent. A simple uncomplicated fibromyoma, however, may occasion pain during menstruation, during pregnancy, and by pressure upon adjacent structures. During the premenstrual phase a large interstitial fibroid sometimes causes considerable pelvic discomfort. Also during menstruation the normal uterine contractions may be colicky and painful, especially with an interstitial or submucous tumour in process of expulsion into the uterine cavity. During pregnancy, increased vascularity of the uterus affects an interstitial fibromyoma in its wall and thus increases any pelvic discomfort that may be present. A fibroid in these circumstances may become tender irrespective of the presence of 'red degeneration' (see p. 458). Finally pain is produced by incarceration of a fibroid uterus within the pelvis and pressure upon adjacent vessels and viscera.

Pressure effects

*Type of
fibroid
causing
pressure
effects*

When a fibroid tumour by reason of its position or size is incarcerated in the pelvic cavity, symptoms of pressure upon adjacent structures are liable to occur. Cervical or retroperitoneal growths are the most likely to cause trouble of this kind, but occasionally an interstitial single fibroid of the posterior wall or a pedunculated subperitoneal tumour may become impacted below the sacral promontory and give rise to pressure symptoms.

*Pressure on
bladder*

The bladder is perhaps the viscus most commonly affected, but this organ is able to adapt itself to circumstances in a remarkable manner, and only with cervical or impacted tumours without any range of movement are vesical symptoms likely to occur. The commonest of these is frequency of micturition, usually painless. Retention of urine and 'retention incontinence' are uncommon and in most cases are associated with large cervical growths displacing the bladder upwards and stretching the urethra. Chronic retention and cystitis are rarely associated with uterine fibroids. Acute retention is most likely to occur either just before or during the menstrual function, on account of slight increase in size from temporary congestion.

*Pressure on
ureter*

A ureter is not uncommonly displaced by a retroperitoneal fibroid tumour growing between the layers of the broad ligament; but it is seldom that such a ureter is so seriously involved as to result in hydro-ureter or hydronephrosis.

*Pressure on
rectum*

The rectum may be compressed by an incarcerated pelvic tumour, leading to constipation and haemorrhoids. Calcification of an impacted fibroid in an elderly subject has occasionally exerted sufficient pressure upon the rectum to produce chronic intestinal obstruction.

Pressure upon blood-vessels, more particularly the external iliac vein at the pelvic brim, sometimes produces varicosity of veins or oedema in the corresponding lower extremity. Generally the blood-vessels are sufficiently protected by muscular tissues to escape much direct compression. The same applies in even greater degree to the nerves of the lumbo-sacral and sacral plexuses. Only retroperitoneal tumours exert pressure so direct and so severe as to cause symptoms. Therefore pain such as sciatica, associated with a large fibromyoma, is not necessarily attributable to the presence of the tumour, and relief of pressure is not always associated with relief of the sciatic neuralgia. Large abdominal fibromyomas displace not only the intestines, but also the stomach, seriously impairing gastric and hepatic functions; the cardiac and respiratory mechanisms are also not uncommonly embarrassed.

*Pressure on
blood-vessels
and nerves*

*Pressure on
stomach and
intestines*

Reproductive function

Reference has already been made to the effect that fibroids exert upon the reproductive functions (see p. 450). Not only is absolute

Sterility



FIG. 43.—Fibroids complicating pregnancy. The uterus is the seat of multiple fibroid tumours, one occupying the lower segment. The uterus has been laid open exposing an early ovum in its cavity: the embryo is visible in the amniotic sac

sterility more common, but relative sterility is increased. A woman with an interstitial or submucous fibroid in her uterus is more likely to abort or be the subject of a premature labour.

*Abortion and
premature
labour*

Apart from this tendency, pregnancy complicated by fibroids is liable to other complications. In addition to the risk of necrobiosis or 'red degeneration' a submucous fibroid may also be infected during labour, or slough as the result of damage to its capsule. Some submucous fibroids are extruded during the puerperium, this occurrence being commonly associated with severe bleeding. The presence of a tumour in the uterus increases the risk of a malpresentation; if it is in the

*Complications
during
pregnancy*

*Malpresenta-
tion*

*Obstruction
and
haemorrhage*

lower uterine segment or cervix it will also obstruct labour, and during the third stage may interfere with physiological retraction and cause severe post-partum haemorrhage. An interstitial or submucous fibroid may therefore prove a serious hindrance to the reproductive function; on the other hand most subperitoneal, and some interstitial, tumours cause no trouble; several pregnancies and labours have been safely negotiated by the subjects of such growths. Munro Kerr showed that some fibroid tumours discovered in patients during the early months of pregnancy, which might reasonably be thought to introduce an element of danger, have later been lifted out of the pelvic cavity and have not caused any difficulty whatsoever.

(5)—Course and Prognosis

Many cases of uterine myoma run their course without interfering with the patient's comfort or mode of life. As women with fibroids in the uterus may be ignorant of the fact, it is impossible to produce reliable statistical evidence of the proportion of these tumours which cause trouble by their size or secondary complications.

*Rate of
growth*

The question not uncommonly arises how long has a tumour been present. The rate of growth of a fibromyoma varies within considerable limits and depends not only on its vascular supply but also on the age of the patient and the position of the tumour within the uterus. Large single interstitial fibroids with well vascularized capsules develop more rapidly than multiple subperitoneal and especially pedunculated tumours, and intercurrent pregnancy favours rapid growth. Fibroids also appear to grow more rapidly in young patients in the late twenties or early thirties than in the woman approaching the menopause. The removal of a myoma by myomectomy in a young patient may therefore prevent hysterectomy for a large tumour at a later date. The fact that the growth of fibroids diminishes as the menopause approaches should not, however, influence the question of surgical treatment when urgent or severe symptoms indicate that it is necessary. The presence of fibroids tends to delay the onset of the menopause.

*Influence of
age**Liability to
complications*

Some types of myoma are liable to special risks; thus the submucous polypoidal tumour is liable to slough, the single interstitial fibroid to undergo cystic or necrobiotic degeneration, and the subperitoneal pedunculated growth to twisting of its pedicle or to become adherent to adjacent tissues. The risk of malignant metaplasia occurring in a fibromyoma is about 1 per cent. Apart from this danger the likelihood of a fibroid being a direct cause of death is not great, in spite of the severe degree of secondary anaemia sometimes present when a patient first applies for treatment.

*Malignant
change*

Lockyer estimated that about 45 per cent of patients with uterine fibroids present symptoms calling for treatment. Although they do not dispose to a fatal issue, there can be little doubt that they are responsible for a considerable amount of ill-health. The same author

has stated that these patients constitute about 10 per cent of all gynaecological cases.

(6)—Diagnosis and Differential Diagnosis

The diagnosis of a uterine fibroid or fibroids does not, as a rule, present much difficulty. In the case of an abdominal tumour factors such as obesity, nervous rigidity, or co-existing ascites of extraneous origin may be troublesome factors, but in most instances the presence of a hard, rounded, median or paramedian swelling will prove most commonly to be a uterine fibroid. If doubt exists about the nature or relations of a tumour, examination under deep general anaesthesia is useful and advisable.

With large tumours difficulty may arise in distinguishing between an ovarian new growth and a uterine fibroid. The ovarian tumours are cystic in the proportion of about nine to one, and therefore the solidity of a doubtful tumour of pelvic origin is in favour of uterine origin and of a fibroid. It is important to establish, by means of bimanual examination, the relation of the cervix uteri to the tumour. The latter should be lifted out of the pelvis by a hand placed upon the abdomen. If the cervix is raised by this manœuvre it may be accepted that the new growth is of uterine origin or adherent to the uterus. Subperitoneal pedunculated fibroids as a rule do not allow of such a clear deduction, especially when the 'stalk' is long. The diagnosis between such a tumour and an ovarian cyst is rendered more difficult should the former happen to be elastic or cystic from degeneration.

With medium-sized fibroids, either within the pelvis or just above the pelvic brim, the continuity of the cervix with the tumour mass is easily established by combined abdominal and vaginal examination. In cases of doubt it is inadvisable to use the uterine sound. Information that may be gained as to the length of the cavity is not reliable owing to distortion of, or encroachment upon, the cavity by the tumour. This statement, however, does not apply to the diagnosis of submucous and especially polypoid fibroids, in which the sound may be of considerable value.

In the diagnosis between submucous or interstitial tumours which have produced uniform enlargement of the uterus, and pregnancy of the same size, care is necessary. Consideration of the menstrual history, the state of the breasts and cervix, and the presence of intermittent contractions or foetal heart-sounds will usually decide the diagnosis. Only in cases of deliberate concealment of pregnancy when false information upon the menstrual function is supplied, or when a fibroid uterus is complicated by early pregnancy, is difficulty likely to arise. The Aschheim-Zondek test, and radiography during the later months, are of value. Although changes suggesting pregnancy may be present in the breasts and cervix in a patient with fibroids in her uterus, the degree of such changes is important in diagnosis. With uterine fibroids a little secretion may be expressed from the nipple, or the cervix may

*Abdominal
fibroid*

*Diagnosis
from ovarian
new growth*

*Use of
uterine
sound*

*Diagnosis
from
pregnancy*

even be a little softened, but not to a degree comparable with the conditions during pregnancy.

*From
carneous mole*

An early pregnancy, which has terminated as a carneous mole or missed abortion, may closely simulate a submucous myoma. The organ is enlarged, rounded, and firm, and the associated irregular uterine bleeding may lead to an error in diagnosis. In cases of doubt therefore it is always advisable to explore the uterine cavity under anaesthesia, after dilatation of the cervix, before resorting to any serious surgical procedure. A uterine souffle is not uncommonly audible over a large interstitial uterine fibroid, very similar to that heard over the pregnant uterus. Ovarian tumours are commonly dumb on auscultation.

*Cervical and
retro-
peritoneal
fibroids*

Cervical and retroperitoneal fibroids may be recognized by their immobility and the displacement of adjacent viscera which they produce. Cervical growths may almost fill the pelvic cavity but rarely extend higher or as high as the umbilicus. The body of the uterus can commonly be palpated on the summit of the abdominal tumour, and care must be taken to identify it as such and not to mistake it for a small subperitoneal fibroid. With both retroperitoneal and cervical fibroids some difficulty may occur in recognizing and locating the vaginal cervix, as the cervix is often pulled upwards and forwards behind or even above the pubes. The anterior vaginal wall is correspondingly flattened and lengthened. Menstruation is not affected by the presence of cervical or retroperitoneal fibroids. The symptoms which cause the patient to seek advice are associated with the mechanical dislocation of adjacent viscera, for example retention of urine and increasing constipation.

*Histological
diagnosis*

Although the nature of an abdomino-pelvic or pelvic tumour may be suspected, the exact diagnosis of a uterine fibromyoma can only be made by expert microscopical examination after its removal. For example, an adenomyoma produces identical physical signs, and its precise nature may be evident only when it is examined on section. In the same way the various degenerations to which fibroids are subject may be anticipated from a consideration of the symptoms, but definite proof can only be supplied after removal.

*Intra-pelvic
fibroids*

The diagnosis of intrapelvic uterine fibroids depends in great measure upon the care with which a bimanual examination is conducted and the interpretation of the physical signs. A submucous or interstitial fibroid produces nothing more than uniform enlargement of the uterus which must be distinguished from such conditions as molar pregnancy, chronic subinvolution, diffuse uterine fibrosis, and carcinoma of the corpus uteri. Exploration of the uterine cavity under anaesthesia by means of the gloved finger, uterine sound, or diagnostic curettage may be the only means of reaching a diagnosis. A subperitoneal fibroid situated in the recto-uterine fossa (pouch of Douglas) or in one of the postero-lateral quadrants of the pelvic cavity can be recognized by its physical characters and its relation to the uterus. These should

suffice to distinguish it from other pelvic swellings such as a small ovarian cyst, adherent or inflamed uterine appendages, inflammatory effusions, haematocele, and faecal accumulations in the rectum or pelvic colon.

Submucous myomas in process of expulsion from the uterus through the external os sometimes cause difficulty in diagnosis. The recognition of a smooth rounded fibroid polypus in the vagina is not difficult when the long pedicle can be felt in the cervical canal by the examining finger. When a tumour fills the vagina and has undergone necrotic changes the resemblance to a fungating carcinoma of the vaginal cervix may be very close. Indeed, the diagnosis may not be possible until the attachments of the new growth have been verified by examination under anaesthesia, and, if necessary, removal of the necrotic growth. The association of the latter with a profuse stinking discharge commonly complicates the diagnosis still further.

*Fibroid polyp
in vagina*

*Diagnosis
from
carcinoma of
cervix*

Care must also be taken not to regard a submucous fibroid in process of extrusion through the external os as inversion of the uterus, and vice versa. This mistake, which may happen during the puerperium if the possibility is not recognized, should be avoided by careful bimanual examination and the use of the uterine sound. The small openings of the uterine (Fallopian) tubes upon the surface of the inverted uterine body are diagnostic points of importance but may be obscured by congestion of the tissues.

*From inverted
uterus*

The onset of malignant metaplasia may be suspected when a fibromyoma begins to grow or produce haemorrhage *de novo* after the menopause. Such tumours are usually also tender and painful on pressure.

*Malignant
change*

(7)—Treatment

Fibroids are common, but the discovery of one of these tumours by no means indicates the adoption of active measures. It is sometimes wise, in the absence of symptoms, to withhold information of the existence of a fibroid from the patient. Only when the tumour causes symptoms, or by reason of its size or position is likely to cause inconvenience in the future, is it necessary to intervene. In approximately 50 per cent of cases no therapeutic measures are necessary.

The growth of fibromyomas in the uterus cannot be prevented, and, apart possibly from measures to promote an artificial menopause, their rate of growth cannot be controlled. The treatment of these growths therefore is either symptomatic, specific, or surgical.

Symptomatic

Symptomatic treatment may be required for the relief of uterine haemorrhage, pain, or symptoms caused by pressure on neighbouring organs. Haemorrhage in the form of menorrhagia may be severe, and appropriate measures should be taken to obtain an immediate effect before a grave secondary anaemia is established. In the control of

*Treatment of
haemorrhage*

- Ergot* uterine bleeding associated with fibroids, drugs are not always successful, and ergot in this connexion is very unreliable. Hydrastis and the salts of cotarnine are more dependable both from a haemostatic and sedative standpoint. Hydrastis is prescribed as the liquid extract in doses of 30 to 60 minims, or as the dry extract in the form of a 2-grain pill.
- Hydrastis*
- Cotarnine* Cotarnine may be administered either as the phthalate (styptol) or as the chloride (styptarnin, stypticin). The dose of styptol is $\frac{3}{4}$ grain three or four times daily by the mouth. In an emergency cotarnine chloride may be given hypodermically in doses of 1 to 2 minims of a 10 per cent solution. A useful and convenient method of administering hydrastis and cotarnine together is in the form of tabloid hydrastine compound and cotarnine hydrochloride (hydrastine hydrochloride $\frac{1}{4}$ grain, extract of ergot B.P. 1914 $\frac{1}{2}$ grain, cannabine tannate $\frac{1}{2}$ grain, cotarnine hydrochloride $\frac{1}{4}$ grain). Potassium chlorate in a dose of 5 grains three times daily is sometimes valuable in controlling temporarily excessive menstrual haemorrhage associated with fibroids. To obtain an immediate effect in checking a severe bleeding, reliance must be placed upon a hot vaginal douche and, should this fail, plugging the vagina. The temperature of the douche must be at least 116° F., and two or three pints of an antiseptic solution should be used. In plugging the vagina to control haemorrhage two important points must be observed, namely, efficiency of the packing and the avoidance of sepsis. To ensure efficient packing the operation should be conducted in a good light with the patient in the lithotomy position. The fornices of the vagina are firmly plugged first with a long strip of bismuth or iodoform gauze, and the rest of the vagina is then closely packed. Sepsis is avoided by removing the plug after twenty-four hours, by administration of an antiseptic douche, such as diluted dettol, before the introduction and after removal of the gauze, and by scrupulous attention to surgical technique even during an emergency.
- Potassium chlorate*
- Vaginal douche and plugging*
- Testosterone* Favourable results in the control of uterine haemorrhage associated with fibroids have recently been obtained by the use of synthetically prepared male hormone. Loeser, by means of intramuscular injections of 50 mgm. of testosterone propionate (perandren) on alternate days produced complete cessation of menstruation and an atrophic endometrium. He stated that 'during the functional rest in which the uterus received no stimulation by female hormone, the fibromyoma decreased in size'. A total dose of 500 mgm. of the propionate was required to effect this result. Hormone therapy on these lines, or by means of chemically pure preparations of the corpus luteum (e.g. progestin or proluton), offers a promising field of therapeutic investigation in the symptomatic treatment of fibroids.
- Treatment of anaemia* After a series of severe haemorrhages the haemoglobin may fall as low as 25 per cent, and every effort must be made by the use of transfusion, iron salts, and liver extract to restore the deficiency before surgical treatment directed to the radical cure of the tumour is contemplated.

Pain is not a common symptom with uterine fibromyoma, but if associated with degeneration or coexisting inflammatory lesions it may be relieved by such measures as heat applied to the pelvis in the form of hot prolonged vaginal douching, infra-red rays, or kaolin poultice. Pain resulting from pressure within the pelvis is not readily amenable to symptomatic treatment apart from the use of analgesics. Occasionally it is possible to dislodge a fibroid uterus partly impacted in the pelvis and place it above the sacral promontory.

Treatment of pain

Retention of urine associated with an impacted tumour is most likely to occur during a menstrual period and is a clear indication for subsequent surgical treatment to prevent recurrence. The patient should be kept in bed and catheterization carried out until the emergency is over.

Retention of urine

Specific

The specific treatment of uterine fibroids includes irradiation of the uterus, either by X-rays or by radium, which, in properly selected cases, can undoubtedly secure cessation of menstrual and irregular haemorrhage. It is also reported that in some cases a fibromyoma has diminished in size after irradiation. These effects result mainly from atrophy of the ovaries with complete destruction of the Graafian follicles. They are the result of the artificial menopause and, like the menopause which follows surgical ablation of the ovaries or the natural menopause, are accompanied by flushings and other vasomotor disturbances.

Irradiation

Cases suitable for X-ray therapy are small or medium-sized fibroids in women of the menopausal age in whom uterine haemorrhage is the predominant symptom. Large tumours palpable above the pubes and all growths in which degenerative changes or coincident pelvic inflammatory disease is suspected are better dealt with surgically. Treatment by irradiation has the advantages that, provided cases are selected with care, there is no risk to life and it is possible for the patient to follow her usual activities during the time she is under observation. Irradiation of fibroids should only be carried out by those who are equipped with the special apparatus required and who have the requisite expert knowledge. The method is not without danger and I have seen an extensive epitheliomatous ulcer of the abdominal wall develop on the site of a burn following the application of X-rays to control uterine haemorrhage associated with a large abdominal fibroid. The haemorrhage had ceased but the large tumour was still present. Should irradiation fail and surgical intervention be required, the operation is rendered more difficult and correspondingly more dangerous by reason of the extensive and often dense perimetric adhesions almost invariably produced by X-rays.

X-ray therapy

Dangers of X-rays

Radium introduced directly into the uterine cavity, after dilatation of the cervical canal under anaesthesia, is an alternative radiotherapeutic method and in some ways is preferable to X-ray therapy in that its effect is produced primarily upon the endometrium rather than the ovaries, and there is no risk of producing superficial burns.

Radium therapy

Dose 50 mgm. of radium bromide with a filter equivalent to 2 mm. of lead are introduced into the uterine cavity in a tube applicator and left for seventy-two hours. The applicator is sterilized by boiling, and after its introduction the cervical canal and vagina are packed with gauze which should remain *in situ* until the radium is removed. An anaesthetic is not required for removal as the cervix remains open while the radium applicator is in the uterus. A thread is commonly attached to the applicator to facilitate removal. A vaginal antiseptic douche—not one containing iodine or mercury—should be given daily for the following four weeks. Usually one application of radium, on the lines indicated, effects a permanent cessation of haemorrhage; occasionally a second application may be needed.

Surgical

Indications When fibromyomatous growths are so large as to produce symptoms of pressure within the pelvis or to form a tumour palpable from the abdomen, when palliative measures fail to check haemorrhage, when rapidly growing myomas occur in young subjects, and when a new growth shows evidence of renewed activity after the menopause it is generally agreed that surgery offers advantages over other methods.

Myomectomy and hysterectomy With such indications it is advisable to enucleate the growth from the uterus (myomectomy), or to remove the uterus containing the new growth either wholly (total hysterectomy) or in part (subtotal hysterectomy).

Choice of operation Although hysterectomy for fibroids has been practised successfully for many years, the tendency now is to regard the conservative technique of myomectomy as the operation of choice, certainly in the case of single growths in young women. Nearer the age of the menopause and in the presence of multiple tumours the decision is more debatable, but even in the fourth decade some surgeons prefer the conservative operation to a method which condemns the patient to the discomforts of an artificial menopause.

Mortality Myomectomy compares favourably with hysterectomy in primary mortality. In a series of 400 consecutive cases published by Bonney the operative mortality was 1·7 per cent. In 741 myomectomies performed at the Mayo Clinic the mortality rate was 0·9 per cent. The surgical risk of hysterectomy for fibroids is between 1·5 and 2 per cent. About 2·5 to 3 per cent of patients require a secondary operation after myomectomy either from a recurrence of symptoms or because of the growth of fresh tumours: and 'of women who have undergone myomectomy and are within the age of child-bearing, and wishful to have a child, 39 per cent may be expected to conceive' (Bonney). Of the labours after myomectomy 75 per cent are normal, Caesarean section being necessary in the remaining 25 per cent. The conservative operation should be performed only when the uterus and its adnexa are otherwise healthy. It is quite unjustifiable, for example, in the presence of associated pelvic endometriosis, perimetritis due to coexistent salpingo-oöphoritis,

Influence on pregnancy and labour

and when malignant disease is suspected. The operation may be performed by either the abdominal or vaginal route. The vaginal operation is employed for the removal of submucous tumours, especially when pedunculated. *Vaginal method*

The patient is placed in the lithotomy position and, after adequate exposure of the vaginal fornices with suitable specula, a transverse incision is made in front of the vaginal cervix through the anterior vaginal fornix. The bladder is dissected upwards, and the anterior wall of the uterus sectioned in the middle-line by means of straight scissors from the external os upwards, as high as may be required. The uterine cavity is explored with the gloved finger and, if the submucous tumour is too large to be removed *in toto*, its size is diminished to permit of its extraction in fragments (*morcellement*). Before a fibroid tumour can be enucleated from the uterine wall, either by the abdominal or vaginal route, it is necessary to incise the capsule. Unless this is done the operation may prove unnecessarily difficult and haemorrhage may be excessive.

Abdominal myomectomy should be performed whenever possible through a single uterine incision, with secondary interstitial incisions to enucleate growths which cannot be reached by the former. Haemorrhage can be prevented by the use of Bonney's clamp forceps or by spinal analgesia, although I prefer not to use clamp forceps but to deal with bleeding points *seriatim* as necessary. This obviates the danger of subsequent bleeding from vessels which at the time of operation have not demonstrated their presence. In all methods it is important to eliminate by careful suture all dead spaces left after enucleation of the tumour, to observe accurate haemostasis, and to employ only catgut which in strength, absorbability, and asepsis is above suspicion. *Abdominal method*

Hysterectomy, either subtotal or total, is probably the operation most often performed in the surgical treatment of fibroids, in spite of the advantages offered in selected cases by the conservative alternative of myomectomy. *Hysterectomy*

The subtotal operation with modern methods of technique is simple and comparatively easy. Whether performed by the routine method or by the more rapid technique of Kelly its mortality is low, and there is little doubt that the surgeon who removes only a few uteri in the course of his practice, or who fears trouble with the ureter or deep pelvic veins, will continue to use it. In expert hands total hysterectomy, i.e. removal of both the corpus and cervix uteri, is, in the opinion of most pelvic surgeons, the better operation. The mortality is no higher, post-operative drainage is better, and the risk of carcinoma developing subsequently in the cervical stump is eliminated. The latter is no theoretical risk as more than 1,500 cases of cancer of the cervix after subtotal hysterectomy are recorded. In the course of twelve months, three examples have come under my observation, an experience which would influence the views of even the most staunch advocate of the subtotal method. If the total operation is not always adopted as a *Mortality*
Incidence of carcinoma in cervical stump

routine, subtotal hysterectomy should be limited to nulliparae and to cases of uterine fibroids complicated by evidence of weakness of the pelvic floor, in which removal of the cervix predisposes to subsequent inversion of the vagina. It is usual to conserve one or both ovaries if healthy, but in practice this does not always prevent the patient from experiencing the functional sequelae of suppression of menstruation.

For the surgical details concerning the operations of total and subtotal hysterectomy, reference should be made to page 488.

3.—LIPOMYOMA

(*Synonyms*.—Myolipoma; fibrolipomyoma; lipomatosis of fibroids)

- Definition* 1587.] Lipomyoma is a fibromyoma exhibiting fatty metamorphosis, or metaplasia of fibrous or myomatous tissue, as distinct from fatty degeneration.
- Aetiology* The aetiology of the presence of fatty tissue in a myomatous uterine tumour as an example of vital activity quite separate from fatty degeneration (see p. 457) is unknown. In the few cases recorded (Ley) the patients were parous, middle-aged women, not obese, with nothing in the clinical history to provide a clue to the conditions which favour this very rare lesion.
- Morbid anatomy* A lipomyoma to the naked eye presents a yellow or yellowish-white appearance. The 'whorled' characters of the normal fibroid are lost, or but faintly evident. The consistence is soft, and remains so even after several days' immersion in a hardening solution. Microscopical examination of frozen sections stained by Sudan III shows large fat-globules within the muscle-fibres. The nuclei of the latter are retained.
- Clinical picture* In the few records available, the symptoms appear to be those associated with ordinary uterine fibroids. In Ley's case, the incidence of post-menopausal haemorrhage was an important feature. The menopause had occurred six years previously, and haemorrhage had been in progress for twenty-one days per month over a period of twelve months before the patient came under observation. Lockyer's patient had frequent and profuse uterine bleeding for three years before the uterus was removed. Local pain is apparently not a feature of lipomatosis in fibroids, an interesting observation in view of the tenderness usually associated with tumours undergoing fatty degeneration.
- The course and prognosis of lipomyomas appear to be identical with those of fibroids. No evidence is available to demonstrate an increased tendency to malignancy.
- Diagnosis and differential diagnosis* Lipomatosis in a fibromyoma occasions no special symptoms, and its physical signs are identical with those of uncomplicated fibroids. Differential diagnosis from a fibroid is therefore impossible.
- Treatment* In recorded examples, the lesion has been discovered after removal

of the uterus. The tumour is benign, and therefore there is no reason, given suitable indications, why lipomyomectomy should not be adopted.

4.—ADENOMA

1588.] Adenoma is an epithelial tumour of endometrial origin, due to hyperplasia of the uterine glands and involving either the corpus or cervix uteri. In the corpus two types may be recognized: (i) simple adenoma, and (ii) papilliferous adenoma. In the cervix a simple adenoma only has been described. *Definition and types*

(1)—Simple Adenoma of Corpus Uteri

(*Synonyms*.—Adenomatous hyperplasia; adenomatous polypus; mucous polypus)

The existence of a true neoplastic hyperplasia of the corporeal endometrium, as opposed to the 'adenomatosis' associated with metropathia haemorrhagica (Schröder's disease, see Vol. VIII, p. 513) and some cases of chronic inflammation of the endometrium, is recognized. Such hypertrophy may be diffuse, or localized, when it constitutes a mucous polypus. A true adenoma of the corporeal endometrium is not associated with evidence either of abnormal ovarian function or of chronic inflammation of the endometrial stroma. The new growth occurs in virgins, nulliparae, and multiparae, and the cause is unknown. *Mucous polypus*

Adenoma of the corpus uteri, whether diffuse, or localized as an adenomatous or mucous polypus, is usually associated with uterine haemorrhage. Menstrual bleeding is increased, especially with the diffuse type of growth. A simple mucous polypus commonly produces a slight intermittent haemorrhagic discharge. Abnormal bleeding, excessive leucorrhoeal discharge, and occasional menstrual pain are the only symptoms. *Clinical picture*

Although not malignant, an adenoma of the endometrium shows its neoplastic character by a tendency to recur. Symptoms of haemorrhage and increased discharge are likely to return in the course of a year or so after curettage. When the lesion has been in evidence for some time hypertrophy of the muscular wall of the uterus is not uncommon. *Course and prognosis*

The diagnosis is made by microscopical investigation of the tissue removed by curettage. This may consist of large fleshy masses which to the naked eye not uncommonly suggest malignancy. Under the microscope the glands are enlarged and lined by simple regular epithelium and are separated by a hyperplastic normal cellular stroma which does not show any evidence of inflammation or mitosis. *Diagnosis*

In treatment curettage may be employed first and in some cases will suffice, but should haemorrhage recur it is advisable to introduce a tube of radium into the uterine cavity. In young patients a dose of *Treatment*

<i>Radium</i>	2,000 mgm. el. radium hours is given; in women approaching the menopause this may be increased to 3,500 mgm. el. radium hours.
<i>Hormones contra-indicated</i>	Being a true neoplasm, adenomatous hyperplasia of the endometrium is not likely to be influenced by hormone therapy directed to the inhibition of ovarian function.
<i>Treatment of mucous polyps</i>	Mucous polyps which are pedunculated and protrude through the cervical canal into the vagina may be twisted off. As these small growths are not uncommonly multiple, it is advisable to curette the endometrium at the same time. All such polypi should be submitted to careful microscopical examination as occasionally an apparently innocent growth may prove to be carcinomatous.

(2)—Papilliferous Adenoma

(*Synonym.*—Villous tumour of the endometrium)

<i>Aetiology</i>	Papilliferous adenoma of the endometrium is a comparatively rare uterine lesion allied histologically to a simple adenoma and, like the latter, of obscure aetiology.
<i>Morbid anatomy</i>	The tumour forms a large solid papilliferous or polypoid growth which may completely fill the uterine cavity. To the naked eye it resembles a villous papilloma of the bladder and for this reason was termed villous tumour of the endometrium by Bland-Sutton. The whole of the corporeal endometrium may be involved or the lesion may affect one wall only. Microscopically the gland tubules of the endometrium show much hypertrophy and hyperplasia. They do not as a rule infiltrate the uterine wall and the epithelium is usually constituted by a single layer of columnar cells. In some cases both microscopical and clinical evidence of a malignant tendency is shown by this growth. Some of the tubules show epithelial proliferation and the nuclei may be mitotic. In other cases, though histologically simple, the adenomatous elements exhibit definite infiltration of the muscular wall and the growth recurs locally. Such types should be regarded clinically as malignant.
<i>Microscopical appearances</i>	
<i>Malignancy</i>	
<i>Clinical picture and course</i>	Papilliferous adenoma of the corpus uteri develops after the menopause. The youngest case on record was in a woman aged 52. Its presence is indicated by a more or less continuous blood-stained discharge which is rarely excessive. Nulliparae appear to be more commonly affected than multiparae. Pain is not common and the only symptom apart from bleeding to attract the attention of a patient is the occasional presence of a troublesome and profuse thin serous vaginal discharge. The symptomatology is practically identical with that of cancer of the body of the uterus, with which papilliferous adenoma has many points in common. The prognosis, in view of the possible local malignant tendencies of even histologically benign growths, is uncertain and it is advisable to adopt a cautious attitude.
<i>Diagnosis</i>	The diagnosis of villous tumour of the endometrium is readily made by microscopical examination of the tissue removed by curettage in an elderly woman who presents the above symptoms. The latter, and

also the naked-eye appearance of the tissue removed from the uterus by the curette, suggest carcinoma, and it is not until the pathological report is received that the true nature of the growth is revealed. Difficulty may be experienced in deciding whether or not epithelial proliferation of the gland tubules is malignant. The point must be decided by such criteria as the staining of the cell, the presence of active mitosis, and evidence of invasion of the uterine wall by the recognition of muscular elements permeated by the glandular tubules.

Diagnosis from carcinoma

Diagnosis of malignancy

Owing to the possible malignant tendencies of papilliferous adenoma of the endometrium, it is advisable not to temporize when the condition has been recognized. The uterus should be removed by total hysterectomy, or the condition treated by radiotherapy on approved lines (see pp. 469 and 474).

Treatment

(3)—Adenoma of Cervix Uteri

Adenoma of the cervix uteri is a benign epithelial new growth originating in the cervical glands of the uterus and maintaining the same epithelial type of growth.

Definition

Adenoma of the vaginal cervix is rare and few instances have been recorded. In a case described by Lockyer, a possible pre-existing inflammatory factor was present in that the patient was sterile, and the cervical tissues surrounding the growth revealed a well marked inflammatory reaction. The tumour causes enlargement of the cervix, the vaginal surface epithelium being replaced by a deep red papillary and fissured growth. Microscopically the tissue shows a mass of branching tubular spaces lined by a single layer of columnar cells with basal nuclei and containing mucus. Where the growth approaches the epithelial surface the epithelium is lost and the tumour exposed.

Aetiology

Histology

In the few recorded cases the symptoms are mainly haemorrhage and vaginal discharge. In Lockyer's case profuse leucorrhoea had been present since childhood and the patient complained of haemorrhage, bleeding on coitus, and a constant dragging pain in the pelvis.

Clinical picture

The condition must be distinguished from a simple cervical erosion (pseudo-adenoma), epithelioma, and tuberculous cervicitis. The surface bleeds more freely than an erosion, and the tissue is more resistant than a cervical carcinoma and not friable. Microscopy of an excised fragment will confirm the nature of the lesion.

Diagnosis

Vaginal hysterectomy has been performed for this growth, but such treatment would appear to be rather drastic and unnecessary for a tumour recognized to be local and benign. Amputation of the cervix should suffice.

Treatment

5.—SARCOMA

(1)—Definition

1589.] Sarcoma of the uterus is a malignant tumour of mesoblastic origin arising from the connective-tissue elements in the uterus, either in the body or cervix.

(2)—Aetiology

In common with new growths of the same type in other organs the aetiological causes which govern the growth of a sarcoma in the uterus are unknown. Various factors, such as heredity, trauma, chronic inflammation, and sterility, have been cited which might have a predisposing influence. No conclusive evidence, however, is available to prove the truth of any of these statements.

*Age
incidence*

Sarcoma of the uterus occurs during infancy, but the first period of relative frequency is during the early years of puberty. From then onwards the tendency increases until a maximal incidence is reached during the fifth decade. Sarcoma of the uterus is therefore essentially a disease of the menopause and to a less extent of puberty and infancy. This would appear to indicate a lack of stability or imbalance between the factors which stimulate and inhibit cell growth. The influence of gonadotropic and other hormones in this connexion is receiving increasing attention.

(3)—Morbid Anatomy

Sarcoma arises in the uterus by malignant metaplasia either of the connective tissue or of the myomatous cells of the myometrium, the embryonic connective tissue of the endometrial stroma, or from the endothelium of blood-vessels and lymphatics (endothelioma and perithelioma). It is rare in the uterus and constitutes less than 0.5 per cent of the malignant growths of this organ. The corpus uteri is more commonly involved than the cervix in the proportion of 5 to 1. The type of sarcoma most often observed occurs in the muscle wall either as a primary growth or, more commonly, as malignant metaplasia in a pre-existing fibroid (see p. 459). Both 'circumscribed' and 'diffuse' types are described.

*Circumscribed
type*

The circumscribed constitutes a rounded solid tumour, homogeneous on section and dull yellow in colour. It is soft and friable, and this not uncommonly results in the production of irregular spaces containing blood-stained fluid. Microscopically the growth is commonly a mixed-cell type, round cells, spindle cells, and giant cells being present in the same tumour. Circumscribed sarcomas, although interstitial in origin, may later become subserous, or submucous and polypoid, as is the case with fibromyomas. This important fact emphasizes the necessity for careful microscopical investigation of all uterine or polypoid growths, and especially those which recur. Sarcomatous uterine polypi appear to favour the occurrence of uterine inversion, possibly as the result of infiltration of the uterine wall by malignant cells. Sarcomatous metaplasia of uterine fibroids has already been described (see p. 460).

*Microscopical
appearances*

Diffuse type

The diffuse type of sarcoma is very rare and causes uniform enlargement of the whole uterus which may form a large tumour resembling the pregnant organ. The growth on microscopical section shows round cells or spindle cells in combination, as in the circumscribed type.

Sarcoma of endometrial origin also occurs in diffuse and circumscribed types but is much rarer in this site than in the myometrium. The diffuse form is seen most often near the fundus uteri and forms a soft friable fleshy growth which eventually involves the whole endometrium and may occlude the cervical canal, resulting in a pyometra or haematometra. Histologically a diffuse sarcoma of the endometrium is of the round-celled type.

*Sarcoma of
endometrial
origin*

Circumscribed sarcoma of the endometrium occurs (i) as a nodule which may become polypoid and extend through the cervical canal into the vagina where it forms a soft red or grey sloughing tumour, and (ii) as a soft vesicular growth in relation with the cervix and known as 'grape-like sarcoma of the cervix' or 'sarcoma cervicis botryoides'. The appearance of this remarkable growth is characteristic; it forms a mass of rounded branching and polypoid growths springing from the vaginal surface and filling the vagina, the whole resembling a bunch of grapes. The soft consistence is due to oedema, and the unusual mode of growth is attributed to rapid development of the sarcoma at numerous points, unfettered by pressure by reason of its anatomical position. This tumour, which in some cases appears to contain striped muscle fibres and hyaline cartilage in addition to round and spindle sarcomatous cells ('chondro-rhabdomyosarcoma'), is highly malignant and grows with extreme rapidity. One patient, a child of two, died at the end of six weeks from the onset of symptoms.

*Circumscribed
sarcoma of
endometrium*

In addition to the above types, examples of 'mixed' sarcomas occur in the uterus as in other organs, due to differentiation of the embryonic type of sarcomatous cell into tissues of a higher grade of development. In this manner examples of myxosarcoma, lymphosarcoma, lipomyxosarcoma, angiosarcoma, chondrosarcoma, rhabdomyosarcoma, and adeno-chondro-sarcoma are produced.

*Mixed
sarcomas*

Endothelioma and perithelioma cannot be recognized from other types of malignant uterine tumours by the naked eye. Microscopical examination is requisite to show the relation of the columns of endothelial cells to the internal or external tunics of the blood-vessels. They possess a low grade of malignancy.

*Endothelioma
and
perithelioma*

Tumours which appear to show both sarcomatous and carcinomatous tendencies are occasionally found in the uterus. They are allied pathologically to the endotheliomas and are termed 'carcinoma sarcomatodes'.

*Carcinoma
sarcomatodes*

(4)—Clinical Picture

The clinical picture of sarcoma of the uterus is similar to that of carcinoma, the prominent symptoms being haemorrhage, discharge, and pain and varying with the type of case. Thus bleeding and pain are earlier and more severe with sarcomas involving the endometrium than with circumscribed interstitial tumours. Polypoid growths are always associated with severe irregular bleeding and a profuse offensive and watery discharge. Occasionally a large cervical sarcoma exists

Symptoms

without apparently causing any symptoms until it fills the vagina and even appears at the vulva. With sarcomas of the uterine wall the clinical symptoms and signs closely resemble those of fibroids. The uterus increases in size, the enlargement at first being uniform but later irregular and nodular. A souffle is audible over very vascular tumours. Rapid growth in a uterine tumour suspected to be a myoma should always suggest the possibility of sarcoma, especially if associated with irregular uterine bleeding (metrostaxis). The probability is greater when these symptoms develop after the menopause. A clinical feature of some importance is the early appearance of such constitutional symptoms as anaemia, loss of weight, cachexia, and insomnia. These are rapidly progressive and out of proportion to the primary symptoms of uterine haemorrhage and discharge. Sarcomatous tumours necrose easily and become infected with septic organisms. Veit stated that 85 per cent of the mortality associated with sarcoma is the result of sepsis and cachexia. Metastases, not only in the vagina and uterine adnexa but also in the lungs, liver, and retro-peritoneal glands, are common and early. The symptoms of sarcomatous metaplasia in relation to fibroids received consideration in the section devoted to those tumours (see p. 464).

Constitutional symptoms

Infection

Metastases

(5)—Course and Prognosis

Grades of malignancy

The malignancy of uterine sarcoma is high and the prognosis correspondingly grave. Sarcoma of the endometrium appears to be somewhat less malignant than the other types, the average duration being about three years. The extreme degree of malignancy of 'grape-like sarcoma of the cervix' was mentioned on page 477. Probably the least dangerous form of sarcomatous tumour is that which develops in relation with a fibroid. Round-celled sarcomas exhibit the highest degree of malignancy and giant-celled growths the lowest. In some cases growth appears to be held in abeyance for a variable time; it then suddenly develops apace and proceeds to a fatal termination within a few weeks. Metastases usually occur at an earlier period with sarcoma than with carcinoma. Endothelioma and perithelioma compare favourably with other types of sarcoma as regards prognosis. Patients have remained well for over four years after removal of a uterus containing these tumours.

Metastases

Endothelioma and perithelioma

(6)—Treatment

Preventive

No methods of preventing the growth of sarcomas in the uterus are known. The only available prophylactic measure is surgical removal of all large uterine fibroids and especially those in which there is reason to suspect degenerative changes. Two per cent of such tumours show early sarcomatous metaplasia.

Specific Irradiation

Treatment other than surgical has hitherto not been attended by any great measure of success. An occasional cure is claimed for radio-therapeutic methods, treatment being on the same lines as that employed for carcinoma of the uterus (see p. 487). A case of 'grape-sarcoma' of

the cervix in an infant under my observation responded to treatment with radium and the child was alive two years after the first application. In a few cases colloidal lead preparations (lead glycine) have given good results. *Lead*

Total extirpation of the uterus and its adnexa by the abdominal route *Surgical* as early as possible offers the best chance of cure. The only contra-indication is evidence of metastases in other organs, local extension of the uterine growth to adjacent organs, and cachexia so extreme as to render radical treatment not only dangerous but useless. Hysterectomy should be followed by radiotherapy on 'Erlangen' lines.

6.—CARCINOMA

1590.] Carcinoma of the uterus is a malignant new growth arising in the epithelium of the uterus, either cervix or corpus, infiltrating the tissues in which it originates, and spreading by direct continuity and permeation of lymphatics to adjacent organs and lymphatic glands and by means of metastases (emboli) in the blood and lymphatic circulations to distant parts of the body. *Definition*

The uterus and the breast are the two organs in the female most likely to be attacked by this disease, the liability being almost the same in each. It has been estimated that of women who reach the age of thirty-five and over, almost 4 per cent die of carcinoma of the uterus. The reason for this high incidence has been sought in the trauma and chronic inflammation to which the organ, and especially the cervix, is liable. That these are by no means always constant factors is shown by the appearance of cancer in the corpus uteri and in the apparently healthy cervixes of some nulliparae. That the uterus is subject to senescent changes at a comparatively early age, namely, the menopause, has also been cited as possibly of aetiological significance. Cancer of the uterus, however, is not unknown in the second and third decades of life and a remarkable instance of cervical carcinoma has been recorded in a child of two and a half years (Adams). Recent investigation into the carcinogenic properties of the sex hormones suggests a possible relation between the activity of these substances and malignant growths of the sex organs, the uterus and breast. Work on these lines would appear to offer a promising field. *Incidence*
Predisposing factors
Menopausal changes
Carcinogenic actions of sex hormones

Cancer occurs in the cervix uteri much more often than in the corpus. Records from necropsies show an incidence of 95 per cent of cases involving the cervix and 5 per cent only the body of the uterus; clinical figures, however, provide a greater frequency of corporeal cancer, 11·25 per cent being given by Wilson. Carcinoma of the cervix and of the body of the uterus differ both pathologically and clinically in so many respects that these growths are with advantage considered separately. *Relative incidence in corpus and cervix*

(1)—Carcinoma of Cervix Uteri*(a) Morbid Anatomy*

Carcinoma of the cervix may arise either from the epithelium of the vaginal portion or from the mucosa lining the cervical canal, the latter being termed endocervical carcinoma. The cervical epithelium shows a marked tendency to undergo metaplasia, especially in cervixes which are the seat of inflammatory catarrh and endocervicitis. The columnar epithelium lining the cervical canal normally terminates at

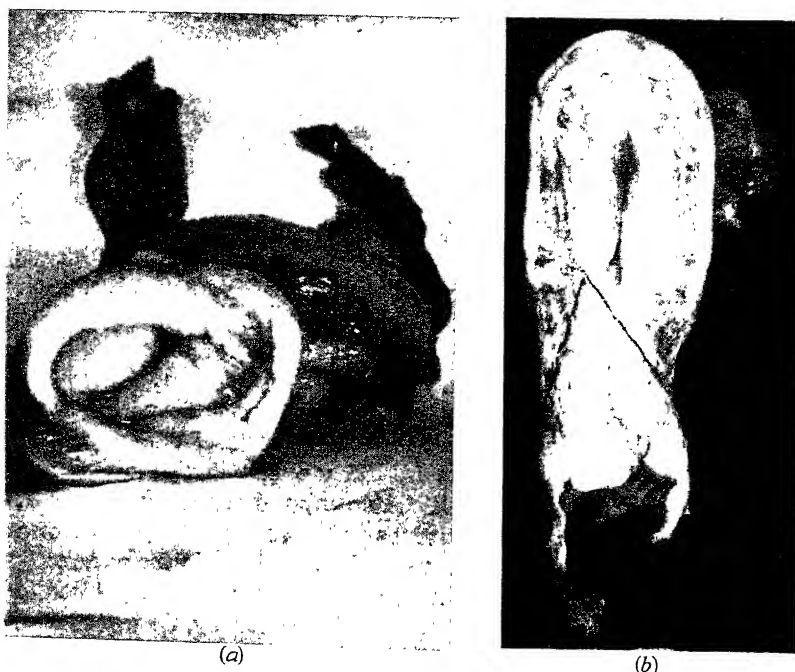


FIG. 44.—Endocervical carcinoma. The vaginal cervix is fissured, but no evidence of extensive malignant invasion is evident from this aspect. In (b) is shown the same uterus in sagittal section: note the extensive involvement of the cervix by the tumour, in spite of the fact that little evidence of such growth is shown in (a)

the external os but, as the result of metaplasia to a squamous type, the great proportion of all cervical carcinomas, including the endocervical tumours, are squamous-cell growths. The precancerous metaplasia sometimes associated with cervical erosion and ectropion of the vaginal cervix has been termed 'leukoplakia' of the cervix by Hinselmann and others. By means of the colposcope, an instrument which provides binocular magnification of the cervical field, these leucoplakic patches may be inspected in the living subject.

Squamous-celled carcinoma of the cervix arises from the deep layers of the epithelium and forms cellular columns which permeate into the sub-epithelial tissues. The cells forming these columns have been differentiated into spinous, transitional, and spindle-celled forms accord-

*Squamous-
celled
carcinoma*

ing to the particular layer of epithelium from which they originate. *Histological types*
 Spinous-celled carcinoma appears to be the least and spindle-celled the most malignant of these histological types.

Carcinomas of the cervix uteri do not as a rule present cell-nests or epithelial 'pearls' as in similar growths elsewhere. This is due to the poor development of the keratin layer in normal cervical epithelium. The central portion of the epithelial buds may degenerate, leading to the formation of pseudo-acinous spaces lined by squamous epithelium. This must not be described as an adeno-carcinoma.

Another type of pseudo-glandular growth is provided by the development of a squamous-celled carcinoma in association with the follicular type of cervical erosion. The malignant follicles are lined by non-secreting squamous epithelium instead of the columnar secreting cells of a true adeno-carcinoma.

Adeno-carcinoma of the cervix uteri is rare as contrasted with *Adeno-carcinoma*
 squamous-celled carcinoma. Microscopically it appears as a mass of branching glandular tubules lined by a single layer of columnar secreting epithelium, and developing either in an 'inverting' or 'everting' manner according to the direction of growth towards or away from the centre of the individual acinus. Adeno-carcinoma of the cervix is much less malignant than the squamous-celled types and has little tendency to invade the parametrium as is the case with squamous-celled carcinoma. In extensive growths the superficial layers are ulcerated over large areas. The characteristic appearance is then obscured by widespread inflammatory round-celled infiltration. To obtain sections for microscopical investigation the growing edge of the tumour should always be selected.

(b) *Clinical Picture and Course*

Cancer of the cervix uteri generally assumes one of two clinical types. *Types*
 Either it shows a tendency to formative growth with extensive proliferation of the tissues or it presents from the first a proclivity to erosion and ulceration. More rarely it produces induration and puckering of the vaginal surface of the cervix without ulceration, a clinical type seen occasionally in elderly subjects.

The most common proliferative carcinoma of the cervix is the so-called 'cauliflower' growth of the vaginal portion which forms a nodular mass in relation with either or both lips of the cervix. It projects into the vagina and may be so extensive as to appear at the vulva. The surface is fissured and the growth is soft and very friable, especially in comparatively young subjects. The tumour necroses easily and the surface is commonly covered with a grey layer of dead tissue. Extension is more liable to take place along the vaginal walls than into the cellular *Proliferative carcinoma*
Spread of growth
 tissue at the base of the broad ligaments. Permeation of the vaginal tissues sometimes results in the appearance of a malignant focus at a distance from the main tumour. Superficially this may seem to be a 'contact' growth.

- Endocervical carcinoma* Proliferative carcinoma of the supravaginal cervix (endocervical carcinoma) produces uniform enlargement and a barrel-shaped contour more easily appreciated per rectum than per vaginam, and the cervix is commonly of larger dimensions than the uterine body. Sooner or later necrosis of the carcinoma occurs and, if the growth involves the whole cervix, ulceration into the vagina ultimately follows. A large crateriform cavity is then produced, the apex being at the internal os and the base on a level with the external os. When the whole vaginal cervix is destroyed the walls of this cavity are flush with the vaginal fornices.
- Infiltration* Endocervical carcinomas infiltrate the parametrium at an early date and, in the later stages, fistulous communications with the bladder and rectum are common.
- Ulcerative carcinoma* The ulcerative type of cervical carcinoma is rarer than the proliferative, both in the vaginal portion and in the supravaginal cervix. A primary epitheliomatous ulcer must not be confused with the secondary ulceration just described in relation with endocervical new growths. It possibly begins in a cervical erosion, which it closely resembles in appearance in its early stages. It spreads slowly as a flat ulcer with indurated edges and shows little tendency to permeate the underlying tissues to any great extent. It usually occurs in elderly subjects.

Methods of spread

- Course of spread in lymph glands* All types of cervical carcinoma spread both by direct continuity and by lymphatic permeation and lymphatic emboli. Indeed, the high malignancy of carcinoma in this site depends partly on the complex lymphatic system surrounding the cervix. The first lymphatic gland to be involved is usually one near the crossing of the ureter by the uterine artery; later, the iliac and sacral glands are invaded, and eventually the lumbar, inguinal, and colic groups may be implicated. In approximately one-third of apparently early cases the lymphatic system is found to be involved at operation. Conversely, it is stated that among the inoperable group with extensive local invasion of tissues about one-third do not show any evidence of lymphatic spread. These facts explain why certain clinically early cases rapidly progress to a fatal termination after radium therapy whereas other women with apparently hopeless local growths are cured.

- Clinical picture* The symptomatology of cervical carcinoma is in no sense pathognomonic. Indeed, its initial phases are free from symptoms because they depend upon the secondary necrotic changes arising when the tumour has reached some size. Early growths are occasionally detected as the result of a chance examination, e.g. as a preliminary to treatment in a contraceptive clinic, or by the routine examination of cervixes removed during operations for prolapse. The earliest symptom is usually haemorrhage, irregular and unconnected with menstruation which commonly is uninfluenced by the presence of the tumour. The bleeding in the first instance is not severe and not uncommonly occurs during defaecation, travelling by rail or motor, and especially on coitus. The
- Haemorrhage*

latter symptom is very significant and always indicates the necessity for a careful local investigation of the genital tract. Haemorrhage alone as an initial symptom is present in about 41 per cent of cases (Wilson).

A second important symptom is discharge. At first this is thin and watery, possibly stained brown by blood pigment, and not offensive. It is constant and therefore disturbs the patient, and in proliferative growths may be very profuse. In the later stages it is not only profuse but very offensive. Its irritating characters produce a secondary dermatitis of the vulva and genito-crural folds. Pain as a rule is not an early symptom of cancer of the cervix uteri. Its incidence signifies either an extensive growth with permeation and blockage of lymphatics or co-existing inflammation of the tumour as the result of infection. As the growth progresses general symptoms become more obvious. Anaemia and cachexia appear as the haemorrhages increase in severity and the discharge becomes more profuse and offensive from extensive necrosis. There is no great loss of weight and many women with extensive growths appear well nourished.

Discharge

Pain

Anaemia and cachexia

Invasion of the bladder is shown first by frequency of micturition which later becomes urgent and painful, the final result being the production of a vesico-vaginal fistula. Blocking of a ureter by pressure or carcinomatous involvement is followed by impaired renal function and hydronephrosis. Infection of the endometrium and partial obstruction of the cervical canal by the tumour leads to the accumulation of pus, blood, and necrotic tissue in the uterine cavity, a condition termed pyometra. This is usually accompanied by fever and occasional discharge of pus from the vagina. When the rectum is extensively invaded by growth, a recto-vaginal fistula usually develops.

Urinary and renal symptoms

Pyometra

Invasion of rectum

Death is commonly the result of asthenia following upon increasing anaemia and cachexia. Occasionally a fatal result is brought about by a sudden severe haemorrhage from an eroded blood-vessel, ascending infection of the kidneys from cystitis, or general peritonitis from infection of the peritoneum with pyogenic organisms from the genital tract.

Cause of death

(c) *Prognosis*

Unless treated, carcinoma of the cervix uteri, as of other organs, proceeds to an inevitable fatal conclusion. This result is reached on an average in a year and a half to two years from the first appearance of symptoms. Age, according to statistics, does not appear to have the influence that was originally thought, and young patients if anything are at an advantage in this respect. The type of growth is to some extent a factor in prognosis, the most malignant being spindle-celled epitheliomas of the endocervix. Spinous-celled carcinomas of the cauliflower type, and the indurated scirrhous forms occurring in elderly women, are of a lower grade of malignancy. Epitheliomatous ulcers of the vaginal cervix also show a comparatively low power of extension.

Influence of age

Effect on prognosis of type of growth

The prognosis of cases submitted to either radiotherapeutic or surgical treatment varies with the degree of involvement of the tissues by the

*Classification
for evaluation
of treatment*

cancerous growth when first seen. As a basis of classification for the evaluation of treatment and prognosis the grouping adopted by the Radiological Committee of the Hygiene Section of the League of Nations has now been universally in use for some years. Modifications have been suggested by Heyman of Stockholm, but here the original scheme is adopted. This may be stated as follows. Stage I: The malignant growth is limited to the cervix, the uterus being mobile. Stage II: The growth has spread into one or more vaginal fornices, with or without infiltration of the uterus, which is still mobile. Stage III: (i) The parametrium on one or both sides is infiltrated by nodules of growth extending to the pelvic walls; mobility of the uterus is impaired or absent. (ii) The vagina is extensively infiltrated by carcinoma, although the uterus may be mobile. (iii) The pelvic lymphatic glands are the seat of metastases, although the primary growth may be small. (iv) Isolated metastases are present in the lower part of the vagina. Stage IV: (i) There is massive infiltration of the parametrium on both sides of the pelvic walls, with fixity of the uterus. (ii) The whole vagina is infiltrated, with fixity of the primary growth. (iii) There is involvement of the bladder or rectum. (iv) Metastases are present in distant organs.

The prognosis is infinitely better in stages I and II, whatever method of treatment is adopted, than in the comparatively hopeless groups III and IV. The inclusion of these latter groups in assessing the absolute curability rate of cases submitted to radiation therapy is liable to produce a false impression. In a series of 507 patients treated in British hospitals with radium between the years 1921 and 1926, 58·9 per cent of those in the early stage were alive and well at the end of five years. Of the borderland group, i.e. stage II, only 10·6 per cent had survived. Of the 'inoperables' (stages III and IV), which constituted 75 per cent of the total, only 6·7 per cent were alive (Eden, Lockyer, and Whitehouse). Similar results have been published from the Institut du Radium in Paris (Lacassagne) and the Radiumhemmet in Stockholm. At the latter, the five-year survival rate for all grades of cervical cancer treated by radiological methods varied between 20·4 and 27·1 per cent. Lacassagne obtained as high a curability rate as 86 and 42 per cent in grades I and II respectively.

In cases submitted to surgical as distinct from radiological treatment, other factors, such as operability and primary mortality rate, must be taken into consideration. In a series of 466 cases of hysterocolpectomy (Wertheim's operation) published by Bonney in 1934 the operability rate is given as 63 per cent. This figure is high and is probably not universally reached. The primary mortality varies from 10 to 21 per cent according as extensive dissection for involved lymphatic glands is or is not necessary. On the five-year basis, the survival rate also varies from 51 per cent of cures in 'gland-free cases' to 21 per cent only when the lymphatics are involved. The prognosis of carcinoma of the cervix treated by operation is well stated in the following words:

'The results of surgery, reckoned on the basis of five years' freedom from recurrence, are best expressed by saying that it succeeds in keeping cancer-free for five years two out of every five patients operated upon and one out of every four seen' (Bonney).

(d) *Diagnosis and Differential Diagnosis*

It is of the utmost importance, in view of the results of treatment and prognosis, to recognize uterine cancer at the earliest possible moment. This can only be done by rigid insistence upon a careful local physical examination aided by the use of suitable specula, and by biopsy of doubtful tissues in all women who present symptoms suggesting the possibility of carcinoma. To shirk the responsibility of arriving at a correct diagnosis and to waste time by the use of symptomatic treatment is reprehensible in the highest degree. In all cases of irregular bleeding from the uterus at or about the menopausal age, it is better to transgress on the side of excessive care and to regard the cause of all such bleeding as malignant until it is proved to be otherwise.

In the diagnosis of carcinoma of the vaginal cervix, the presence of a firm nodular elevated patch, dark purple in colour, irregular on the surface, and dull in appearance, should always arouse suspicion. On contact the area may bleed freely, as distinct from the oozing from numerous minute points associated with a simple erosion. Moreover the tissue is friable, a diagnostic feature of the first importance. The association of a nodular indurated area on the cervix with ulceration of the tissues, friability, and free haemorrhage on contact is sufficient evidence upon which to base a diagnosis of carcinoma. Whenever doubt exists, a section of the suspected area for microscopical investigation should be obtained as soon as possible. This is best done under anaesthesia, the patient being placed in the lithotomy position and the cervix exposed by a vaginal speculum. A small wedge of tissue half an inch in diameter is excised from the edge of the suspected growth and placed immediately in a fixing solution. Schiller claimed that the diagnosis of even microscopical malignant neoplasms is possible by applying a solution of iodine 1 part, potassium iodide 2 parts, and water 350 parts to the cervix before biopsy. The application is made for one minute through a Ferguson's speculum. Healthy tissues are stained brown and carcinomatous foci remain ivory white. The test is not diagnostic of carcinoma but indicates the areas which should be submitted to microscopical examination.

Physical signs

Method of biopsy

Schiller's iodine test

Carcinoma of the cervix uteri must be diagnosed from various morbid conditions of the cervix which bear certain resemblances and may lead to confusion. A cervix which is deeply lacerated, enlarged, and everted as the result of obstetric trauma (ectropion) is liable to be mistaken for a malignant growth. Especially is this so when it is hard from diffuse fibrosis and complicated by an erosion which bleeds slightly on contact. The tissue, however, is not friable, the colour is pink instead of purple, and the bleeding as seen through a speculum is localized to a number

Diagnosis from ectropion

- From erosion* of minute points. The same applies to a simple erosion of the cervix without ectropion.
- From tuberculous ulcer* Tuberculous ulceration of the cervix may superficially resemble an epitheliomatous lesion, but the edges of the ulcer are less indurated and the tissue is not friable. Spontaneous bleeding with tuberculous disease of the uterus is rare.
- From syphilitic chancre* Cervical syphilitic chancres may at first suggest a malignant growth, but the clinical history and the presence of other syphilitic lesions should suffice to prevent an error of diagnosis. Resort should be made to biopsy in all cases of doubt. This applies also to the examination of apparently simple adenomatous or mucous polypi when the suspicion of malignancy exists.
- Endocervical carcinoma* Endocervical carcinoma may be suspected when in the presence of suggestive symptoms, e.g. irregular bleeding and discharge, the cervix, examined per rectum, is found to be considerably enlarged. The uterus must be submitted without delay to careful investigation under anaesthesia. This involves dilatation of the cervix and removal, by means of a sharp curette, spoon, or tissue-punch, of sufficient material for microscopical investigation.
- Growths of vaginal cervix* Fungating malignant growths of the vaginal cervix are usually diagnosed without difficulty both from the clinical history and from the very obvious local physical signs. A necrotic and friable simple fibroid polypus in process of expulsion from the uterus to the vagina may, however, occasionally lead to an error in diagnosis. Removal of the necrotic area and exposure of normal fibroid structure, with demonstration of a pedicle in the case of a submucous fibromyoma, will suffice to make the differential diagnosis.
- Diagnosis from fibroid polyp*

(e) Treatment

Preventive

- Cervical hygiene* The prophylactic treatment of carcinoma of the cervix consists in the adoption of what may be termed adequate and sufficient cervical hygiene. There is little doubt that the severely inflamed and deeply lacerated cervix so often the result of obstetric trauma, natural as well as surgical, is a source of grave potential danger in this respect. Chronically infected foci should therefore be removed by diathermy or otherwise; cervical erosions and chronic endocervicitis should be cured by local therapeutic measures or trachelorrhaphy; and cervixes which are so severely damaged as to render recovery practically impossible should be amputated.
- Post-natal examination* Thorough routine post-natal examination will discover many a cervix which in later years may favour the development of malignant disease. The early recognition and treatment of such diseased cervixes is a valuable preventive measure against the growth of carcinoma in this site.

In the section devoted to the treatment of uterine fibroids (see p. 471),

emphasis was laid upon the importance of total versus subtotal hysterectomy as a prophylactic measure against cervical carcinoma.

Specific

Cancer of the cervix is treated specifically by irradiation with γ rays *Irradiation* applied locally by means of radium or 'Chaoul short wave' therapy, and at a distance by radium beams, or Erlangen deep rays.

Radiotherapy has the advantage over surgical treatment in that it is free from the serious initial mortality attached to the operative methods employed for the radical cure of cervical cancer. Further its final results compare very favourably with those obtained with the latter (see pp. 484 and 488). These results are only obtainable when treatment is carried out in properly equipped clinics and by experts with a thorough knowledge not only of technique but of the desiderata and also possible dangers in the individual case. To treat an early and favourable case with an inadequate dose of radium, or without the assistance afforded by a deep X-ray plant or radium beam, is a practice which cannot be too severely condemned.

Before radiotherapy is applied care must be taken to eliminate local sepsis. Irradiation in the presence of infection either of the cervix or corpus uteri (e.g. pyometra) is very dangerous, and such carcinomas must be regarded as unsuitable for this treatment. The presence of haemolytic streptococci or *Bacillus perfringens* is regarded by some authorities as a contra-indication. Irradiation should also be avoided in the case of extensive growths involving the rectum or bladder. Its injudicious use is more than likely to be followed by the development of fistulae. Anaemia and especially leucopenia should be regarded as indications for a smaller dose of γ rays than is usually employed. *Contra-indications to radio-therapy*

Radium is applied to the uterus and parametrium in the form of the sulphate contained in small platinum tubes 0.6 mm. in thickness. This screen will absorb 99.9 per cent of β rays which, unless eliminated, produce necrosis of healthy tissues and 'radium burns'. Other metals, e.g. aluminium, lead, brass, copper, and silver, may be used instead of platinum, but a greater thickness of casing is required. The tubes containing the radium salt are so arranged in relation to the uterine and para-cervical cellular tissues as to effect a satisfactory cross-fire of the rays. Two methods of application are in common use to-day, namely, the Stockholm and the Paris. *Method of application of radium*

The basis of the Stockholm technique is exposure of the malignant growth at frequent intervals to a large dose of radium heavily screened and for a short application. In a type case, three applications of twenty hours are made, the second treatment being given a week after the first, and the third two weeks after the second. The total dose of radium varies between 6,000 and 7,000 mgm. el. hours, one-third being intra-uterine and two-thirds vaginal. The total vaginal dose should not exceed 4,500 mgm. el. hours, if damage to the rectum is to be avoided. In treating cervical carcinoma by the Stockholm technique it is convenient always to have various applicators adaptable to the conformation of the individual growth. *Stockholm technique*

cannot be treated by similar applicators to those suitable for a flattened malignant ulcer or an endocervical growth. Metal tubes, capsules, boxes, and hollow cones in sections form convenient media to contain the requisite number of radium tubes or needles, and these should be available in different sizes and of such thickness as to provide the necessary screenage. The selected applicator containing the radium is enclosed before use in an envelope of cotton-wool and oil silk or india-rubber. After exposure of the cervix by means of suitable retractors, e.g. Heyman's, the external os is identified, the cervical canal dilated, and the uterine tube introduced. The vaginal applicators are then carefully placed against the tumour and kept in position by firmly packing the vagina with gauze. This important step also displaces the rectum from the source of radium emanation and so prevents subsequent proctitis.

*Paris
technique*

The Paris technique adopted at the Institut du Radium differs from the Stockholm in that only one prolonged application of radium is made for a period of five days, a maximal dosage of 8,000 mgm. el. hours being given. Two platinum tubes 1.5 mm. in thickness containing 13.33 mgm. and one similar tube containing 6.66 mgm. of radium sulphate are introduced 'in tandem' into the uterine cavity in a rubber container. Three similar tubes contained in cork or wooden applicators are then placed in the vaginal vault, one being in each lateral fornix and the third against the vaginal cervix. It is advisable to remove, clean, and replace the vaginal applicators daily to avoid sepsis, and to facilitate this the lateral applicators are attached to a metal spring, the apparatus being termed a 'colpostat' (Lacassagne).

*Irradiation
of lymphatic
fields*

Radium applied per vaginam, by either the Stockholm or Paris methods, should always be supplemented by irradiation of the lymphatic fields either by deep Erlangen rays or radium beam. In the case of deep X-rays, six applications are made and the fields so irradiated that the beams cross at the uterus. Voltz at Munich considered the optimal dosage unit for uterine carcinoma to be between 90 and 110 per cent of the unit skin-dose. With a 4-gram radium beam apparatus, it is usual to treat eight fields, two anterior, two posterior, two lateral, and two postero-inferior. The application is made to one area only per day with an exposure varying from three to ten hours. The distance from the skin is 10 cm. and a screen of 1 mm. platinum is employed.

Surgical

Until the advent of radium, the only treatment available for the cure of carcinoma of the cervix was surgical. The results of irradiation in suitable cases are to-day so good that irradiation has largely taken the place of operative treatment, but in some clinics hysterectomy, either by the extended abdominal technique of Wertheim, or by the vaginal route, is still regarded as the method of election when possible. In other clinics surgical treatment is used in conjunction with irradiation with a view to radical removal of the lymphatic field associated with the cervix uteri.

*Wertheim's
hysterectomy*

Wertheim's hysterectomy (Wertheim, 1911) or hysterocolpectomy (Bourne) differs from total or panhysterectomy in that in addition to the uterus and appendages, the cellular tissue in the broad ligaments,

utero-sacral ligaments, and obturator fossae is removed, together with partial resection of the vagina. The cervical tumour is removed in a closed sack of the latter, to avoid infection of the seat of operation. This is effected by means of clamps applied to the vagina.

The operation to be complete and properly carried out requires the skill of an experienced pelvic surgeon. Even in expert hands it is attended by an initial mortality not lower than 10 per cent, and with operators of less experience this figure may easily be doubled. Factors which influence the mortality rate, apart from such obvious risks as possible injury to a ureter and infection of the peritoneum, are such items as unnecessary manipulation of the tissues, clean rapid dissection, and avoidance of haemorrhage. Incomplete operations sometimes erroneously called Wertheim's hysterectomies are not attended by the same initial mortality, but the curability rate on a five-year basis is correspondingly also lower. *Mortality*

Vaginal hysterectomy as usually performed is not so radical an operation for cervical cancer as the extended hystero-colpectomy of the abdominal route. By the use of paravaginal incisions, however, good access can be obtained to the deeper parts of the pelvis, and in expert hands the uterus and appendages can be cleanly excised with sufficient parametrium to effect a radical cure in properly selected cases. *Vaginal hysterectomy*

Symptomatic

In advanced cases palliative measures only are possible. To check spontaneous and severe haemorrhage the superficial layers of a necrosing fungating growth should be removed under anaesthesia with a curette. The base may then be cauterized or coagulated by means of diathermy. Alternatively the growth may be exposed for five minutes to the action of a mixture of equal parts of acetone and solution of iodine, or a one per cent dilution of formalin. In very extensive growths accompanied by much pain and discharge, all that can usefully be done is to keep the surface of the growth clean by constant irrigation with antiseptic solution and to relieve pain by means of morphine or surgical division of the pre-sacral nerve or the pain paths in the spinal cord. In a few cases of advanced growth, irradiation by means of radium may be useful in relieving the patient's discomfort, even if cure is impossible. Care must be taken to avoid such treatment when the bladder or rectum is involved, as the risk of producing a fistula and increasing the patient's discomfort is then considerable. *Treatment of haemorrhage*

Pain and discharge

(2)—Carcinoma of Corpus Uteri

(*Synonym.*—Cancer of the uterine body)

(a) Morbid Anatomy

Cancer involving the uterine body usually produces a hyperplastic growth which in the most common 'tuberous' type forms a fleshy mass of tissue more or less filling the uterine cavity. Less commonly, diffuse 'papillary' or localized 'polypoidal' types are seen. The growth develops *Types*

in relation with the endometrium, often in the upper part of the cavity. It rarely spreads beyond the internal os, and ulceration is uncommon. The disease is slow in development compared with cervical carcinoma, and it is rare for it to produce much enlargement of the uterus. Indeed, in elderly subjects the uterus may be quite small. The organ maintains its normal contour unless and until the growth permeates the uterine wall to the peritoneum, when a nodular tumour results, somewhat resembling a fibroid uterus. This only occurs with advanced growths of long standing.

*Microscopical
appearances*

On section, the tuberous variety presents a smooth creamy-white appearance. The growth projects into the uterine cavity and invades the uterine wall to a greater or lesser degree. It is, of course, not encapsulated. Microscopically carcinoma of the corpus uteri is of the glandular or adeno-carcinomatous type. Very occasionally a squamous-celled primary carcinoma has been described, the result, no doubt, of preceding metaplastic changes possibly associated with chronic inflammation. Two types of adeno-carcinoma of the uterine body are recognized, the tubular and the alveolar. The tubular type consists of proliferating irregular and closely packed glandular tubules which develop either in an 'everting' or 'inverting' manner. The epithelium is columnar, and malignancy is shown by the irregularity in disposition of the cell nuclei, defective staining properties, and the presence of active mitosis. When no proliferation of epithelium occurs, but the gland tubules exhibit a tendency to invasion of the fibro-muscular wall of the uterus, the growth is termed 'adenoma malignum'. Such growths are difficult to recognize under the microscope unless the section shows the presence of muscle fibres between the gland elements. That the growth is locally malignant is shown by its recurrence after curettage. In the alveolar type of adeno-carcinoma the lumina of the glands are filled with many layers of cells, which form branching columns of growth. Degeneration of the most central cells produces the alveolar appearance. Alveolar adeno-carcinomas are more malignant than the tubular forms.

Tubular type

*'Adenoma
malignum'*

Alveolar type

Direct spread

Cancer of the uterine body spreads by direct infiltration of the uterine wall. The growth remains limited to the uterus much longer than is the case with cervical cancer. Ultimately, it extends through the uterine wall to the peritoneal surface. Adhesions are formed and the omentum or even a coil of intestine may become directly involved. Lymphatic spread is late, the glands affected being the lumbar, and occasionally the inguinal, via the round ligaments. In fatal cases metastases may be found in such organs as the liver, spleen, and adrenals. Secondary growths also appear occasionally in the vagina, probably the result of lymphatic permeation or emboli. Pyometra or haemato-pyometra is not an uncommon complication of uterine body cancer, especially in the less malignant forms in elderly women. In some cases the thickness of the uterine wall may be reduced to a mere shell.

*Lymphatic
spread*

Pyometra

(b) Clinical Picture and Course

Corporeal cancer occurs in the nulliparous as well as the parous woman. It has been estimated that the incidence in the former is as high as 20 per cent compared with 4 per cent in cervical cancer. Even in the case of parous patients fertility is lower (parity 2 or 3) than with cervical carcinoma (parity 5 or 6). The age of onset is somewhat later than with cervical growths, most cases occurring during the post-menopausal epoch between fifty and sixty. This does not mean that cancer of the corpus is never seen before the menopause. A few years ago three women in the early forties with corporeal carcinoma were receiving treatment at the same time in the author's hospital clinic. *Incidence*

The symptoms associated with a carcinoma of the uterine body are similar to those of cervical cancer with the important distinction that they are less obvious, and, consequently, more likely to be overlooked by both patient and doctor. The earliest symptom is a slight blood-stained discharge such as is commonly associated with a simple mucous uterine polypus; from being irregular it gradually becomes constant, but is never profuse. The discharge is not offensive and never purulent unless pyometra exists. Before and during the years of the menopause such symptoms may easily be overlooked. Post-menopausal bleeding, however slight, is so important a symptom that it is more likely to impress a patient and bring her under observation. *Discharge*
Post-menopausal bleeding

Pain is not present in the early stages, but the patient may complain of a certain degree of heaviness in the lower abdomen, or pelvic discomfort. Even in advanced cases pain is not necessarily a feature unless the peritoneum or coils of intestine are involved. The later phases are much the same as in cancer of the cervix. The discharge becomes purulent and offensive, haemorrhage is more severe and prolonged, and gradually a state of cancerous cachexia develops. *Pain*

Physical signs are by no means definite. In the majority of cases, the uterine body on bimanual examination will be enlarged. This, however, is not invariably so, and the size of the uterus must be considered in relation to the age and parity of the patient. A small uterus does not exclude the possibility of a malignant focus within its cavity. When the uterus is enlarged the possibility of coexisting fibroids must be envisaged. Mobility of the uterus is not impaired until the later stages of the disease. *Size of uterus*
Mobility

(c) Prognosis

Without treatment, the average life of a patient with cancer of the corpus uteri is two to four years or longer, from the time of onset of the first symptoms. This is more favourable than is the case with cancer of the cervix.

With treatment, either surgical or radiological, a survival rate of 60 per cent at the end of five years may be anticipated. This figure is more than double the five-year survival rate for all stages of cervical cancer.

(d) Diagnosis and Differential Diagnosis

This usually depends upon the microscopical examination of tissue removed from the uterine body by means of a curette or spoon after dilatation of the cervix under anaesthesia. In the presence of suggestive symptoms this most necessary investigation should never be delayed.

Bimanual examination

Bimanual examination of the uterus may or may not show some slight enlargement. The cervix is healthy and, if the patient is elderly, may

Uterine sound

present signs of atrophy. The use of a uterine sound is dangerous when a malignant tumour of the uterine body is suspected. The walls of the uterus may be so soft and thin, especially when pyometra is present, that perforation of the organ is a very real risk. The only information that it will provide is knowledge of the length of the uterine cavity, and the presence of a lesion which possibly bleeds on contact. Neither of these signs is pathognomonic.

Differential diagnosis

Carcinoma corporis uteri must be diagnosed from other morbid lesions which cause slight uniform enlargement of the organ or are associated with slight bleeding and discharge. Such are senile endometritis, papilliferous adenoma of the endometrium, adenomatous or mucous polypi, metropathia haemorrhagica, submucous fibroid or fibroid polypus, chronic metritis or fibrosis uteri, uterine adenomyoma, and retained products of conception or carneous mole. In all these cases careful attention to the clinical symptoms, and the information afforded by exploration of the uterine cavity with a curette, or in some instances the gloved finger, will prevent mistakes in diagnosis. Errors in connexion with the diagnosis of uterine carcinoma are more usually those of omission than of commission. Important symptoms are carelessly disregarded, or physical examination under anaesthesia deferred, no doubt on occasion in deference to the patient's wishes. These should never be allowed to prevail with so much at stake.

Biopsy

The tissue removed from the uterus by means of the curette should all be collected, placed in a suitable fixing solution (e.g. formol-saline 1 per cent) and sent to a pathologist familiar with lesions of the endometrium. The diagnosis between benign and malignant lesions of the uterus may be a matter of considerable difficulty, as will be seen by a reference to the microscopical appearance of corporeal carcinoma (see p. 490).

(e) Treatment

Cancer of the corpus uteri cannot be prevented.

*Specific**Irradiation*

Specific treatment includes the use of radiotherapeutic measures. Many gynaecological surgeons, including those of the British and French schools, generally regard corporeal cancer, in common with adeno-carcinoma of many other organs, as being unsuitable for irradiation. The more highly evolved cell of the adenomatous growth is considered to be less vulnerable to the γ ray than the more primitive

malignant cell associated with squamous-celled carcinoma, but this view is not held universally, and in some clinics radiation therapy is employed for 'body cancers' equally with those invading the neck of the uterus. Thus Voltz has recorded 66 per cent 'five year' successes in a series of forty-three clinically operable patients. Among forty-two clinically inoperable patients 14.3 per cent were free from recurrence at the end of five years. Heyman at the Stockholm Radiumhemmet has also stated that 'in view of our results we cannot agree with the almost universal opinion that radiological treatment of carcinoma of the uterus cannot compete with surgical treatment'. In view of this difference of opinion upon the most suitable therapeutic measure, it would appear best not to adopt a dogmatic attitude, but to select the method most suitable to the individual case. When surgical risk is great by reason of constitutional factors such as obesity and age, or when the growth is extensive, irradiation is probably more suitable. In the presence of co-existing conditions, such as fibroids and tubo-ovarian inflammation, or when the growth is early and the patient physically able to sustain the shock of an operation, surgical treatment may be employed with a very reasonable prospect of immediate and future success.

The irradiation technique is the same for both corporeal and cervical *Technique* growths (see p. 487). The dose of radium employed is from 4,300 to 4,800 mgm. el. hours intra-uterine; and 1,760 mgm. el. hours in the vagina. This dose is reduced to two-thirds in the case of small senile uteri.

Surgical

Since carcinoma of the body is confined to the uterus and does not invade the lymphatic field until comparatively late in its course, it is sufficient to remove the uterus and appendages alone, either by the abdominal or vaginal routes. The hysterocolpectomy of Wertheim with its dissection of the ureters and pelvic cellular tissue is unnecessary, unless there is reason to believe that the growth has extended also to the cervix—a rare eventuality.

Abdominal total hysterectomy would appear to offer advantages over *Hysterectomy* the vaginal route, as the latter, owing to nulliparity or post-menopausal atrophy, not uncommonly presents technical difficulties. In the case of pyometra, or in elderly multiparae, vaginal hysterectomy is preferable to the abdominal operation. Whichever route is adopted, care must be taken not to implant fragments of the growth upon the incisions. Local recurrences are by no means unknown when this precaution is neglected. The risk of expressing malignant cells through the cervical canal during the course of the operation may be prevented by the insertion of a suture through the vaginal cervix to close the external os as a preliminary to hysterectomy. The immediate mortality risk of *Mortality* hysterectomy for carcinoma of the corpus uteri is from 6 to 8 per cent including all cases. In selected series the risk is but slightly above that associated with hysterectomy for fibroids, namely, 1 to 2 per cent.

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UVEAL TRACT DISEASES

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ASSISTANT OPHTHALMIC SURGEON TO THE BIRMINGHAM UNITED
HOSPITAL AND TO THE CHILDREN'S HOSPITAL, BIRMINGHAM

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Reference may also be made to the following titles:

BLINDNESS	GLAUCOMA
EYE EXAMINATION	MYOPIA

1.—DEFINITION

1591.] The uveal tract constitutes the middle or vascular coat of the eye and consists of the iris, ciliary body, and choroid. The three parts, though continuous, present differing clinical pictures in disease and are therefore described separately, but involvement of one portion is often accompanied by the same change in the neighbouring parts.

2.-CONGENITAL ABNORMALITIES

- Coloboma* Coloboma of the iris is a sector-shaped defect situated downwards and slightly inwards, the edges being smooth and rounded. The defect may continue backwards through the ciliary body to the choroid, where it appears as a pale parabolic area seen with the ophthalmoscope. Rarely it may extend as far as the optic disk. The retina over the affected area is also abnormal.
- Albinism* Albinism consists of failure in development of the pigment of the whole uveal tract and also of the pigment of the pigmented epithelium of the retina, associated with defective pigmentation of the hair. (See also Vol. I, p. 271.) The chief symptoms are photophobia and defective vision; nystagmus is usually present. The iris appears pale grey, and light thrown into the eye is reflected through its meshes as well as through the pupil, giving a pink reflex. The fundus is excessively pale and the broad choroidal vessels are unusually prominent. The macular region is more vascular than the rest of the fundus. Treatment consists in the provision of dark glasses for relief of the photophobia.
- Buphthalmos* Buphthalmos (hydrophthalmos) or congenital glaucoma is described in Vol. II, p. 448; and Vol. V, p. 576.
- Congenital anterior synechia* Congenital anterior synechia is an incomplete form of the same malformation and, though often symptomless, predisposes to glaucoma.
- Heterochromia iridis* Heterochromia iridis is seen as sharply defined areas of differing colour and is a hereditary pigmentary variant; it is not of any pathological significance.
- Aniridia* Aniridia is a total absence of the iris. The ciliary processes and suspensory ligament of the lens are usually present but may be abnormal. Cataract is commonly also present.
- Anisocoria* Anisocoria or inequality of the size of the pupils is, in minor degree, a physiological variant. It is most commonly due to a substantial difference in refraction between the two eyes. In the acquired forms the condition signifies interference with the iris muscles or their innervation.
- Persistent pupillary membrane* Persistent pupillary membrane is a failure of complete development of the pupil with persistence of mesodermal strands. These are seen as coloured strands passing from one part of the iris collarette to another and often traversing a small part of the pupil.
- Macular coloboma* Macular coloboma is hereditary and usually bilateral and consists of an oval area about two disk diameters in extent at or near the macula. The centre is atrophic and pale, sometimes containing pigment granules, and the edges are heavily pigmented. The retina is drawn over the hole but may partly sink into it. Vision is reduced in varying degrees. The pathology is uncertain but local ischaemia in intra-uterine life may be a factor. Arachnodactyly (see Vol. II, p. 557) is commonly associated with this condition (Sorsby). Diagnosis should be made from obsolescent macular choroiditis (see p. 510).

3.—INFLAMMATION

(1)—Aetiological Classification

Iritis

1592.] Iritis is sometimes classified according to the nature of the exudate and may be acute or chronic.

Plastic iritis is usually gonorrhoeal in western Europe but often syphilitic in India and the East. The condition is prone to relapse repeatedly and is characterized by a gelatinous exudate leading to the formation of posterior synechiae and often to seclusio pupillae, iris bombé, and secondary glaucoma (see Vol. V, p. 576). *Plastic*

Sero-fibrinous exudate occurs in the common form of iritis, and, though its aetiology is often doubtful, is found in general diseases, such as gout, rheumatism, and diabetes mellitus; in the secondary stage of acquired syphilis; with chronic or subacute infection of neighbouring organs, such as the teeth, tonsils, and nasal sinuses; or secondarily to scleritis or keratitis, such as that due to severe ulcers and to burns of the cornea by molten metals or chemicals. *Sero-fibrinous*

Purulent exudate occurs in metastatic iritis in pyaemia. Otitis media, puerperal pyaemia, and severe exanthemata provide most cases. These often progress to a generalized endophthalmitis. It is also secondary to acute local infection and, in particular, to ulcer serpens of the cornea in association with dacryocystitis, and to corneal ulcer from abrasion especially by coal dust, or from the forward spread of infection of the ciliary region or anterior choroid. *Purulent*

Haemorrhagic iritis follows contused injuries of the globe, and venous thrombosis of the ciliary region or of the venae vorticosae and is then often accompanied by increased intra-ocular tension (thrombotic glaucoma). Diabetes mellitus in the senile, with arteriosclerosis, also gives rise to this type of iritis. *Haemorrhagic*

Granulomatous or nodular iritis is characteristic of three chronic infections, namely, tuberculosis, syphilis, and leprosy. These produce a low-grade diffuse iritis with insidious formation of posterior synechiae (adhesions between the iris and lens), which are often associated with cyclitis and run a prolonged course. The nodules in tuberculous iritis occur most commonly at the circulus arteriosus major and the circulus minor. In secondary syphilis the nodes or papules occur usually at the pupillary margin or at the circulus arteriosus major near the outer periphery. Nodules are also described in leprosy (see Vol. VII, p. 692) though some authorities recognize only a diffuse lymphocytic infiltration of the iris. *Nodular*

Aetiological classification of iritis is unsatisfactory because the causation is often unknown or depends on evidence of disease elsewhere in the body more often than on specific peculiarities in the eye, or is based empirically on the beneficial response to particular lines of treatment

which are not necessarily specific. There is some difference of opinion about the prevalence of tuberculous iritis on these grounds.

*Aetiological
classification
Infective*

A general aetiological classification, however, can be made as follows.

Toxaemic

Sympathetic

(i) Infective: (a) metastatic as in gonorrhoea, syphilis, tuberculosis, malaria, conditions of general septicaemia, and secondary to infection of neighbouring structures such as the teeth, tonsils, nasal sinuses, and middle ear, and in some of the acute exanthemata; (b) due to local infection of the cornea, sclera, ciliary body, and choroid, or by direct penetrating infection by injury. (ii) Toxaemic, as in rheumatism, gout, diabetes mellitus, and dysentery, and in severe general toxæmia including certain specific fevers. (iii) Sympathetic, a chronic or subacute irido-cyclitis following penetrating injury, particularly in the region of the ciliary body, of the fellow eye: also rarely seen in prolapse of the iris after extraction of cataract and in incarceration of the iris after spontaneous perforation of a corneal ulcer; the mode of origin of this condition is still in dispute. (See Vol. II, p. 414.)

Cyclitis and choroiditis

Cyclitis and choroiditis may be classified in the same way on an aetiological basis but are more commonly classified by their clinical appearance.

(2)—Morbid Anatomy

(a) Iritis

*Transudate
and adhesions*

*Seclusio
pupillae*

In iritis a polymorphonuclear or round-celled infiltration of the stroma accompanies the vascular congestion. Inflammatory transudation into the aqueous humour produces a plasmoid aqueous which may embarrass or even obstruct the filtration angle of the anterior chamber; adhesions form between the iris and lens (posterior synechia) and obstruct the normal communication between the front and back of the iris through the pupil. When such adhesions completely surround the pupil seclusio pupillae arises. The pressure of aqueous humour behind may then bulge the iris forward (iris bombé), obstructing the filtration angle and producing secondary glaucoma. Exudate may also cover the surface of the lens in the pupil area (occlusio pupillae) and greatly obscure vision. Adhesion between the iris and cornea (anterior synechia) is more rare but when present disposes to glaucoma. The rupture of recently vascularized posterior adhesions by the use of atropine may result in haemorrhage (hyphaema) in the anterior chamber, and occasionally this may be due to rupture of congested vessels on the surface of the iris. Inflammation in any considerable degree is accompanied by involvement of the ciliary body and/or choroid.

Resolution

Resolution of inflammation is followed by some degree of atrophy and depigmentation so that the stroma of the iris may become thinned, paler than that of the fellow eye, and may transmit reflected light. Atrophy of the iris muscles results in defective pupillary movements.

Bacteriology

Bacteriological investigation is rarely available in iritis. In secondary

syphilis spirochaetes have been recovered from the anterior chamber but in most forms of iritis the responsible organisms have not been identified locally.

(b) *Cyclitis*

Cyclitis shows morbid changes identical with those of iritis and differs only in its clinical appearance and in the significance of the anatomical position of the ciliary body between the iris and choroid. The exudates formed are thrown into three positions: (i) into the anterior chamber where they congregate on the posterior surface of the cornea, often in a triangular distribution, at the lower central part, and are known as keratic precipitates, keratitis punctata, or shortly 'K.P.' (see p. 503); (ii) upon the posterior surface of the lens where they form a membrane obstructing vision and impairing the respiration of the lens which may consequently undergo cloudy swelling and become cataractous; and (iii) into the vitreous, forming fine dust-like opacities. Cyclitis is prone to relapse. The clinical forms are dealt with as irido-cyclitis. A full description of the pathology of irido-cyclitis was given by Parsons.

(c) *Choroiditis*

Diffuse acute choroiditis appears clinically as panophthalmitis, the whole choroid and interior of the eye being rapidly involved in pyogenic infection. Resolution is accompanied by shrinking of the globe from the contraction of fibrous masses in the vitreous humour (phthisis bulbi). Such infection is usually secondary to septic infection by penetrating wounds or to infection in the course of acute septicaemia or pyaemia. Localized acute choroiditis is metastatic and the primary source often indefinite. Sepsis of the teeth, tonsils, or nasal sinuses is the most common source. More definitely tuberculosis and syphilis are responsible for many instances of choroiditis and these forms are described as clinical entities. But in many cases of choroiditis the origin is quite unknown. Resolution results in an area of central atrophy surrounded by a zone of reaction in which there is usually a ring of increased pigmentation. The retina over these areas of atrophy degenerates and vision is consequently affected.

(3)—Clinical Picture, Diagnosis, and Treatment

(a) *Iritis*

In acute iritis toxæmic signs and symptoms of general disease may be present. Pain is felt in the eye and characteristically in the brow and is continuous, aching, or throbbing. There are photophobia and lacrimation. Vision is usually only moderately impaired, in contrast to the greater loss of vision in acute glaucoma.

The lids are often oedematous. There is congestion of the conjunctival and anterior ciliary vessels, the latter producing a circum-corneal zone of short straight vessels, this flush being characteristic of acute iritis.

In the chronic stage the conjunctival congestion may be absent. The eye-ball is tender, particularly in the ciliary region, and movements of the eye are painful.

*Appearance
of eye*

The cornea may be slightly hazy in the acute stage but is brightly clear in the subacute and chronic stages. The aqueous is turbid and may contain a gelatinous exudate. In severe cases pus may collect in the bottom of the anterior chamber forming a hypopyon which shows as a greyish-yellow streak. Coincident cyclitis is shown by the presence of keratic precipitates ('K.P.') on the posterior surface of the cornea. The iris is congested and darker in colour and the intricate pattern is blurred. The pupil is generally smaller than normal and irregular from

Pupil

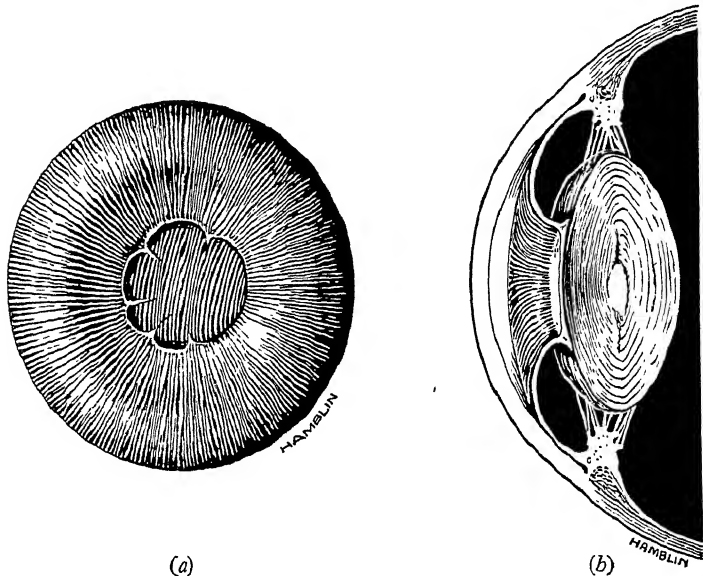
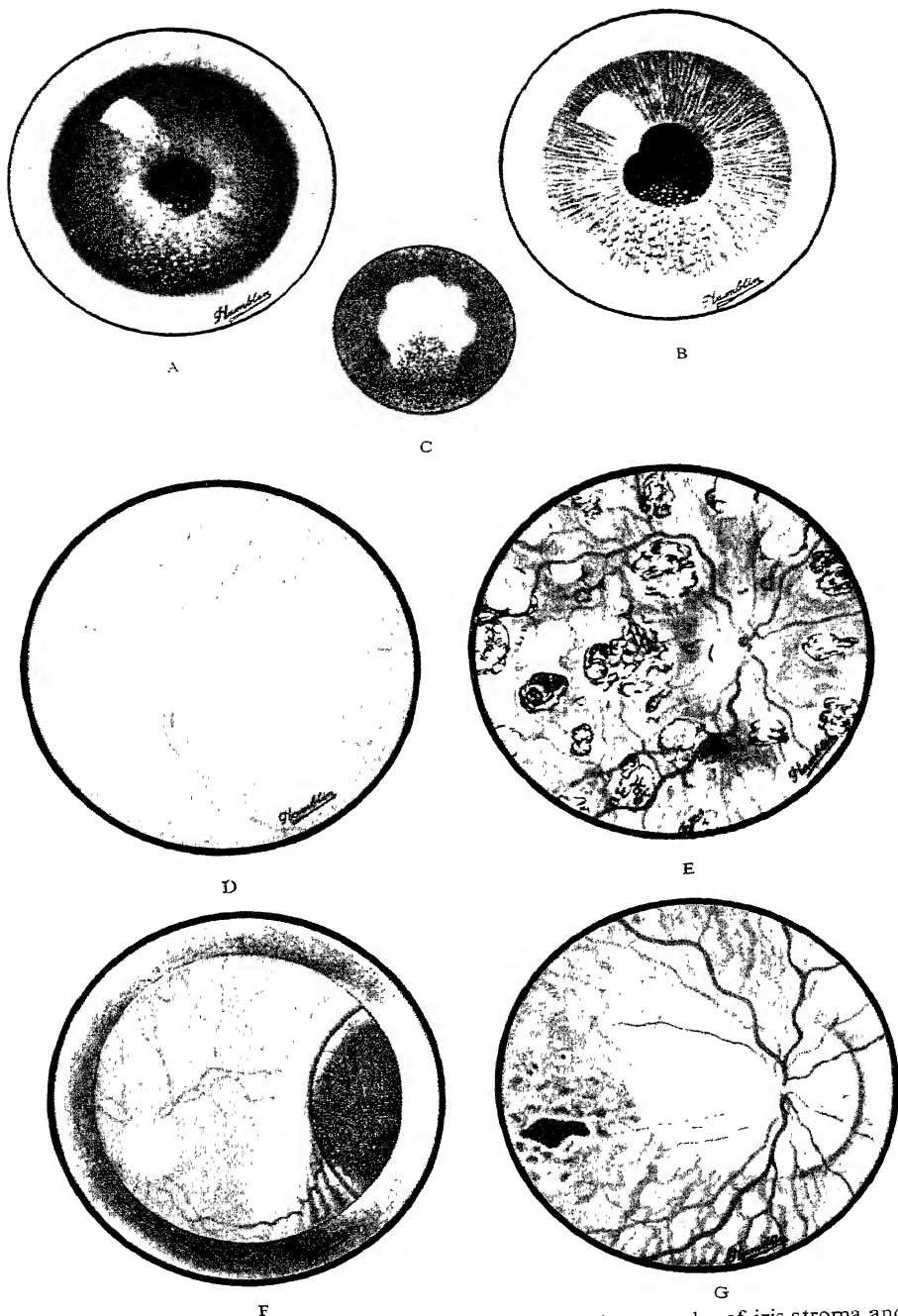


FIG. 45.—(a) Iris bombé and posterior synechiae: anterior view.
(b) Iris bombé, seclusio and oclusio pupillae: sagittal view. Diagrammatic

the presence of posterior synechiae (see Plate XII, A). There is diminished mobility in the reactions to light. Complete adhesion of the margin and posterior surface of the iris to the front of the lens may occur (seclusio pupillae) or exudate may extend across the pupil and obstruct it (occlusio pupillae) (see Fig. 45, b). This process obstructs the passage of aqueous humour from behind and the iris is bulged forward (iris bombé) (see Fig. 45, a and b); as a result the root of the iris is forced into the filtration angle which becomes closed, with resulting increase of intra-ocular tension. In some cases the gelatinous exudate in the anterior chamber blocks the filtration angle producing increased intra-ocular tension with a deep anterior chamber.

Iritis is most common in adolescents and younger adults. First attacks of iritis after the age of forty are not common but recurrence of iritis may persist to any age.



A. Acute irido-cyclitis. B. Chronic irido-cyclitis showing atrophy of iris stroma and depigmentation. C. Irido-cyclitis (under mydriatic), ophthalmoscopic view showing keratic precipitates in focus. D. Acute metastatic choroiditis: the fundus details are slightly indistinct on account of vitreous haze. E. Old disseminated choroiditis (inactive): stage of atrophy. F. Melanotic sarcoma of choroid: showing dark smooth mass projecting, and small fluid detachment of retina below. G. High myopia, showing crescentic degeneration to outer side of disk and macular haemorrhage

Chronic iritis is insidious in onset and may be almost symptomless at first; pain is absent or slight and may not attract attention. The eye may be almost free from congestion of the conjunctival or anterior ciliary vessels, or a mild intermittent ciliary flush may be present. In such cases the usual complaint is slowly increasing loss of sight due to exudate in the pupil and to posterior synechiae. A coincident cyclitis is often present. The chromatophores show little increase and subsequently atrophy with the rest of the iris stroma; consequently the affected iris becomes of lighter colour than its fellow (see Plate XII, B). The incidence of secondary glaucoma may first attract attention to the eye. *Chronic*

Evidence of past iritis may be valuable in the diagnosis of such general diseases as 'rheumatism', osteoarthritis, rheumatoid arthritis, gout, diabetes mellitus, dysentery, malaria, gonorrhoea, syphilis, leprosy, and tuberculosis. Though the eye may not be inflamed, traces of past involvement may be found in irregularity of the pupil with the presence of posterior synechiae. Some mydriatic such as cocaine may be necessary to demonstrate these if the pupil is miotic. These adhesions, at first dark brown, become light grey from the absorption of pigment. The pupillary margin may show an exaggerated dark edge from overgrowth of the pigmented epithelium of the posterior surface of the iris. When mydriasis has been maintained during an acute attack by the use of atropine, the pupil may be perfectly circular and not show any posterior synechiae, but there may be pigment spots on the front of the lens where such have been broken away. *Evidence of past iritis*

The course of an attack of acute iritis is governed by the type and degree of exudation and the effect of treatment. An acute attack seldom lasts for less than two to three weeks or longer than two to three months. Recovery is by lysis but is incomplete for some time after the iris has resumed its normal appearance; recovery is shown by absence of pain and tenderness and of vascular congestion. The diminution of congestion of the anterior ciliary vessels is first noticed far back and the circum-corneal region is the last to recover. The forward recession of congestion indicates the rate and degree of recovery. Photophobia and irritability on examination are among the last signs to disappear. Under early and energetic treatment recovery from acute iritis is usually complete in the initial attack, but relapsing or chronic attacks usually leave permanent defects and are complicated by sequelae. *Course*

When untreated, or inadequately treated, the formation of exudate proceeds to the formation of adhesions with a danger of secondary glaucoma. In lesser degrees posterior synechiae produce irregularity of the pupil and impaired action of the pupillary muscles. Exudate in the filtration angle of the anterior chamber may cause increase of intra-ocular tension. Occlusio pupillae with permanent impairment of vision may follow the collection of exudate on the anterior surface of the lens in the pupil area and, if a major area of the lens capsule is so *Complications*

covered, secondary cataract may follow. Extension of inflammation to the ciliary body often occurs and, in severe cases, may spread to the choroid when a general endophthalmitis may result.

Prognosis

A primary attack of acute iritis if treated early and adequately does not carry a serious risk of severe loss of vision. The pupil can usually be fully dilated and exudates are often entirely absorbed. In recurrent, chronic, or neglected cases with complications, the prognosis may be very serious. Vision is reduced by organized exudates or by the development of glaucoma but is rarely totally lost. The coexistence of cyclitis and/or choroiditis is unfavourable to the prognosis. Diabetic iritis carries an unfavourable prognosis as does infection elsewhere when complicated by diabetes mellitus. (See also p. 506.)

*Diagnosis
from acute
congestive
glaucoma*

Acute congestive glaucoma is the most important disease likely to be confused with iritis. The points of difference may be summarized thus. The onset of glaucoma is often marked by acute pain in the brow and head and vomiting without other general symptoms. Loss of vision is extreme and very rapid, but there may have been premonitory attacks of transient obscuration of vision lasting only a few minutes. Rings or haloes of the colours of the spectrum may be seen round lights but usually the complaint is of a fog or mist. The intra-ocular tension is raised. Supra-orbital pain is usually moderate, as are ciliary and conjunctival congestion which are sometimes slight. The cornea is diffusely and evenly hazy from oedema of its layers, but without keratic precipitates. The anterior chamber is shallow and the pupil inactive and semi-dilated with the vertical diameter often greater than the horizontal. The margin of the pupil is regular and, except in thrombotic cases, does not show posterior synechiae. The iris is congested, and the lens gives a greenish reflection on focal illumination. In the initial acute attack the fundus may be invisible on account of corneal oedema but, if seen, the optic disk is not cupped. In subsequent attacks, or in chronic glaucoma, the disk is cupped and atrophic. On no account should atropine be used. The age is usually over forty, the sex commonly female. (See also Vol. V, pp. 580 and 583.)

*From acute
thrombotic
glaucoma*

Acute thrombotic glaucoma often follows thrombosis of the central retinal vein, occurs predominantly in obese hypertensive subjects between the ages of 55 and 75 years, but closely resembles acute iritis in many ways; pain is constant and severe. There may be transudation from the iris with formation of posterior synechiae; congestion of the iris, conjunctiva, and ciliary region is prominent, the vessels of the iris being engorged and varicose.

*From acute
conjunctivitis*

Acute conjunctivitis is distinguished by the absence of congestion of the anterior ciliary vessels, by the clear anterior chamber, and by the normal colour, pattern, and mobility of the iris, by the normal shape and reactions of the pupil, and by the presence of conjunctival congestion and of a sero-fibrinous or muco-purulent discharge from the conjunctival sac.

Acute episcleritis, scleritis, and keratitis show the characters of a

normal iris but there is engorgement of the anterior ciliary vessels and oedema of the episcleral tissue. Episcleritis is often confined to a sector of the globe and extends backwards for some distance. Scleritis may be sharply localized in patches, and evidence of previous attacks may be shown by thinning of the sclera and slaty-blue areas where the underlying uvea shows through. Keratitis shows opacity or vascularization of the cornea and possibly ulceration. In severe cases of these diseases there is commonly some degree of associated iritis.

*From
episcleritis
and
scleritis*

*From
keratitis*

(b) Cyclitis

Acute cyclitis accompanies most severe cases of iritis. Clinically the signs and symptoms correspond in most respects to those of iritis but there may be greater tenderness over the ciliary region. The characteristic sign is the presence of keratic precipitates, consisting of

Acute

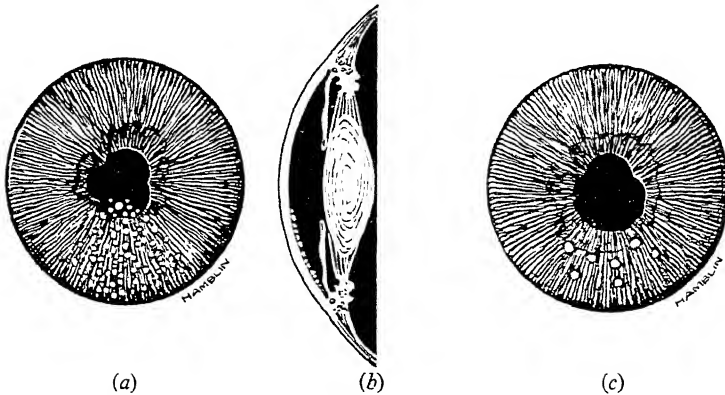


FIG. 46.—(a) Irido-cyclitis: showing posterior synechiae and keratic precipitates. (b) Cyclitis: sagittal section: showing position of keratic precipitates on back of cornea. (c) Irido-cyclitis: with mutton-fat keratic precipitates (possibly tuberculous aetiology)

aggregations of dead leucocytes deposited upon the back of the cornea. 'K.P.' may be extremely fine and translucent and only visible by careful 'K.P.' observation with the aid of oblique focused illumination and a loupe. The spots are usually grey but sometimes brownish; the distribution may be diffuse but is characteristically most prominent in the lower part of the cornea extending upwards towards the centre of the cornea to end in a point, thereby having a triangular shape, apex upwards (see Plate XII, A, B, and C, and Fig. 46, a and b). The aqueous is turbid. Exudate is also present on the anterior, and especially the posterior, surface of the lens, and cells extruded into the vitreous produce a haze of varying density. These exudates obscure vision, the loss of vision being more severe in degree and tending to be more persistent than in iritis.

Loss of vision

Chronic cyclitis or subacute relapsing cyclitis presents a separate clinical picture though some degree of iritis or anterior choroiditis is probably always present. The disease is insidious in that pain,

*Chronic
cyclitis*

photophobia, lacrimation, and injection of vessels may be absent and slowly increasing failure of vision may alone at last attract the patient's attention. For this reason the condition is serious, since treatment may be long delayed.

Course

As a complication of acute iritis a mild degree of cyclitis is not of very serious significance and usually undergoes complete resolution with the iritis under adequate treatment. Recovery is indicated by diminution of the number and shrinking of spots of keratic precipitates which show crenellate edges. Cyclitis as the major infection, however, runs a prolonged course and is prone to relapse.

Three to nine months is a satisfactory period in which to secure quiescence, but obstinate cases defy treatment for as many years and sometimes longer. As the ciliary body forms the major portion of the vascular coat of the eye, vascular transudation is on a more generous

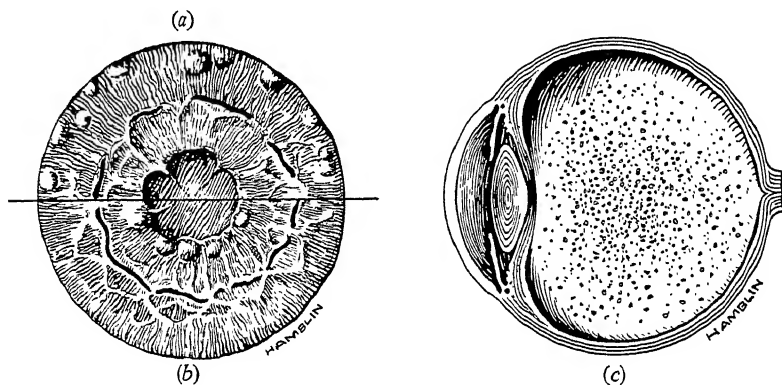


FIG. 47.—(a) and (b) Nodular iritis: (a) tuberculous; (b) syphilitic, secondary stage. (c) Cyclitis complications: vitreous opacities and posterior lenticular exudate

scale so that absorption is slow and often incomplete. The response to treatment is often unsatisfactory and the prognosis correspondingly poor.

Complications

The transudations from the ciliary processes into the anterior chamber may form a very dense film of keratic precipitates which, if permanent, obstruct vision severely. The anterior surface of the lens is less commonly involved; the posterior surface is more often affected, and the exudates may form a dense membrane adherent to the lens which may so impair the osmosis through the lens capsule as to cause degeneration of the lens fibres and secondary cataract. The exudate into the vitreous produces a haze of varying density in the acute stage, thus impairing vision (see Fig. 47, c). In the chronic stage subsequent fibrosis of the vitreous and diminished activity of the ciliary processes from atrophy may cause disorganization of the globe with shrinking (phthisis bulbi). These cases almost always have advanced from cyclitis to generalized uveitis. In lesser degree shrinking of the vitreous may result in detachment of the retina of an intractable type. Cases in which extension of the inflammatory process involves the whole uvea are very grave and are often accompanied first by a condition of secondary glaucoma and

later by decreased intra-ocular tension; in cases of endophthalmitis vision is often totally lost.

The prognosis in cyclitis is worse than in iritis and choroiditis because its progress may be considerable before attracting attention, it is resistant to treatment, subject to relapses, in aetiology even more indefinite than iritis, and its complications are far more damaging to vision.

(c) *Special Forms of Irido-Cyclitis*

In cases of irido-cyclitis aetiological factors are uncertain, but in some cases the clinical picture is sufficiently characteristic to justify a presumptive classification.

Tuberculous irido-cyclitis is usually chronic with subacute exacerbations, is extremely persistent, and liable to recurrence. Anterior choroiditis often co-exists and sometimes is more diffuse or accompanied by a retinal periphlebitis. The disease is insidious in onset and often remains unnoticed for some time. The iritis may be diffuse, or nodular. In the diffuse type extensive posterior synechiae form and are extremely tenacious, and iris bombé may result from ring synechiae. In the nodular type the nodules are most commonly seen in the angle of the anterior chamber in relation to the circulus major and are usually confined to the outer half of the iris (see Fig. 47, a); they are greyish-yellow and about the size of a pin's head. They may break down and produce erosion or holes, and resolution is accompanied by thinning of the stroma in localized areas. The keratic precipitates may be diffuse and of the usual distribution, when they are not distinctive, but sometimes are few in number, large, and yellowish—so-called mutton-fat 'K.P.' (see Fig. 46, c)—and these cases strongly suggest 'K.P.' tuberculosis. Vitreous opacities are dense and slow to resolve even when there is a response to treatment, but many cases are not influenced by treatment. Treatment should be prolonged for months after the disappearance of all vitreous and aqueous opacities as a precaution against relapse.

Bilateral irido-cyclitis accompanied by bilateral enlargement of the parotid gland constitutes the syndrome of uveo-parotitis. The parotids are of a firm woody consistence, painless, and not tender; salivation is not increased as in mumps, and the other salivary glands are rarely involved as in Mikulicz's disease (see Vol. IX, p. 454). There is a slight evening rise of temperature during the stage of parotid enlargement. The irido-cyclitis is not characteristic. A full account of this syndrome was given by Garland and Thompson, and it has been suggested that it is associated with some lesions of the central nervous system (Feiling and Viner). The parotid condition responds well to light doses of X-rays; the irido-cyclitis should receive the usual treatment of tuberculous irido-cyclitis (see p. 507).

In association with syphilide or tuberculide of the face an intractable chronic irido-cyclitis sometimes occurs.

In secondary syphilis there may be a sero-fibrinous irido-cyclitis of

the ordinary type. Its incidence in western Europe appears to be diminishing but it is still common elsewhere. In the secondary stage nodular iritis also occurs, the nodes being chiefly on the inner half of the iris and characteristically on the pupillary margin (see Fig. 47, *b*). Deep-seated nodes occur but do not attract attention so readily. Cyclitis is less frequent and less prominent than in tuberculous cases, and anterior choroiditis still less frequent. Interstitial keratitis of any severity is accompanied by some degree of iritis.

Gonococcal Gonococcal iritis is pre-eminently plastic and produces a gelatinous exudate. Synechiae are numerous and *occlusio* and *seclusio pupillae* are common. Relapses are characteristic. The condition is essentially septicaemic and is often accompanied by arthritis of the same aetiology. Keratic precipitates are rare.

Diabetic Metastatic iritis secondary to septic foci is more frequent in diabetes mellitus, but is not truly diabetic in pathology. Diabetes mellitus, however, induces a haemorrhagic iritis in which the vessels of the iris are extremely varicose; these cases show also vitreous opacities and degeneration in both the retina and choroid.

*Herpes
zoster
ophthalmicus* When herpes zoster involves the naso-ciliary branch of the ophthalmic division of the trigeminal nerve, severe irido-cyclitis is very liable to develop. The absence of normal vascular tone and of trophic impulses makes this type exceedingly resistant to treatment and the prognosis is grave. Hypotension or hypertension of the globe is a common accompaniment. (See also CORNEA, INJURIES AND DISEASES, Vol. III, p. 430.)

*Sympathetic
irido-cyclitis* Sympathetic irido-cyclitis occurs in a healthy eye following perforating injury of the fellow eye, sometimes after a latent quiescence of years but usually within two to six months. (See BLINDNESS, Vol. II, p. 414.)

*Treatment:
general* During the acute stage the patient should remain in bed in a darkened room for one to two weeks. Diaphoretics and diuretics are useful and the bowels should be kept gently open. Diet should be full but digestible.

Medicinal Local medicinal treatment aims at rest, warmth, and diminution of vascular congestion. Atropine sulphate 0.5 to 1 per cent, in the form of drops or ointment, is put into the eye every three hours at first and, when dilatation of the pupil has followed, continued twice a day. Drops of cocaine hydrochloride solution 2 per cent relieve pain and enhance the action of atropine. Synechiae resisting atropine may be broken down by subconjunctival injection of 5 minims of mydricine or by the instillation of laevo-glaucon. Heat is applied either by hot bathing for twenty minutes four or five times daily or by electric heaters or charcoal boxes for similar periods. Diminution of congestion is also assisted by the application of two leeches to the temple; this treatment is especially valuable in cases with gelatinous exudate into the anterior chamber, and whenever the intra-ocular tension is raised. Leeches may be applied every forty-eight hours till the anterior chamber is free from exudate or the intra-ocular tension has fallen. In the absence of leeches blistering of the temple by cantharidin is a good substitute.

In very obstinate cases with increased tension the effect of diathermy is often dramatic; the application to the lids should be for ten to fifteen minutes, using a current of about 600 kilocycles and 400 to 600 milliamperes; the treatment may be repeated daily for a week or more. Lowering of tension is greatest some six to twelve hours after the treatment.

The prolonged use of atropine may ultimately lead to a condition of allergic hypersensitivity of the conjunctiva and of the skin of the lids and face. First apparent as a follicular swelling of the conjunctiva of velvety appearance, it rapidly involves the skin of the lids and face in a brawny oedema. In patients with atropine irritation the atropine should immediately be stopped and scopolamine used instead, but they may, in due course, develop a similar sensitivity to the latter alkaloid. The sensitivity, once acquired, persists throughout life and will recur acutely on the first administration of these drugs even after a lapse of years. Mydricine, however, by subconjunctival injection, may be given without incurring the allergic response.

Pain is relieved by atropine and cocaine, by heat, and especially by using leeches, and is assisted by giving 15 grains of aspirin three times a day or three compound aspirin tablets thrice daily. In severe cases, morphine sulphate $\frac{1}{4}$ grain may be injected at the beginning of treatment, but two leeches are usually more efficacious. Ten-minim doses of tincture of gelsemium may be given if supra-orbital referred pain is very severe. Photophobia is relieved by darkening the room, a shade for both eyes, or darkened spectacles.

Treatment of the underlying cause is important. Septic foci should be eradicated but with discretion and with due consideration rather than as a routine, because a flare-up may follow the sudden release of sepsis. Such foci should be left alone till the acute phase of the eye condition has passed. The general disease of which irido-cyclitis is often but a manifestation requires close attention; in this connexion toxæmia must be treated on general grounds, and has an important effect on the course of the ocular condition. The diathesis of the patient may be helpful in otherwise obscure cases. Specific general treatment is indicated when a clinical type of irido-cyclitis can be recognized. Clinically many cases improve on injections of tuberculin or neoarsphenamine, but it is doubtful if their effect is specific. This response to treatment has led to confusion and the assumption of unproven aetiology, so that the incidence of tuberculous or syphilitic irido-cyclitis varies very widely with different authorities (Foster Moore; Urbanek).

Antituberculous injections consist of the use of O.T. (old tuberculin), T.R. (tuberculin residue), or B.E. (bacillary emulsion). In these the initial doses must be very small, T.R. $\frac{1}{20,000}$ mgm. and B.E. 0.0001 mgm., and gradually increased over a period of three to five months to a full dose of 1 mgm. The maximal dosage employed by many authorities, however, is 0.25 mgm. Care must be taken to avoid local or general unfavourable reactions by too abrupt an increase in dose. This

*Atropine
irritation*

*Local and
symptomatic*

*Treatment of
causal general
disease*

*Specific:
anti-
tuberculous*

form of treatment should be given when the irido-cyclitis has passed its acute stage. In children, daily inunction of the arms with ointment of O.T. 15 per cent or guaiacol 5 to 7 per cent may be preferable to repeated injections.

Anti-syphilitic

Syphilitic irido-cyclitis should receive the usual treatment with potassium iodide and injections of arsenic derivatives alternating with bismuth. Neoarsphenamine is useful in sympathetic irido-cyclitis, the form due to post-operative endogenous infection, and for the irritation resulting from the presence of lens cortex in the anterior chamber. During treatment the urine should be watched for the presence of urobilinogen. In patients who cannot tolerate neoarsphenamine, mercuric chloride may be given intravenously in weekly injections starting with $\frac{1}{84}$ grain and increasing, with doses of $\frac{1}{56}$, or $\frac{1}{42}$, $\frac{1}{28}$, and $\frac{1}{16}$ grain.

Protein shock

Protein-shock therapy is helpful when irido-cyclitis fails to improve under usual treatment, in traumatic cases with perforation, and as a preventive against sympathetic irido-cyclitis. It may consist of intramuscular injections of horse serum or sterile milk, with a first dose of 5 c.c. and subsequently doses of 10 c.c. given on the first, third, seventh, and twelfth days after injury. Except after the first injection, no appreciable febrile reaction follows if the injections are given on alternate days.

Sulph-anilamide

The recent introduction of the sulphanilamide group of substances in the treatment of septicaemia and of autogenous infections generally promises to open a new field in the treatment of irido-cyclitis. Already experience has shown remarkably rapid and complete recovery in cases of uncertain but endogenous aetiology. Although it is too early as yet to know what compound of this nature will prove most efficient and least toxic, it may be remarked that so far sulphanilamide, uleron, and soluseptasine have given satisfactory results: M & B 693 is particularly effective in pneumococcal infections. Care must be taken to ensure a sulphur-free diet for forty-eight hours prior to and during the use of these drugs. Dosage consists of oral administration of 5 grams in the first twelve hours and then 1 gram four-hourly for four to five days. A further course may be given after a week's rest, but careful watch must be kept against the occurrence of polyneuritis. It is not too much to hope that this method of treatment will eliminate the present practice, of doubtful value, of antituberculous treatment so frequently given in cases of unknown aetiology and will stimulate a more rational approach to the treatment of endogenous irido-cyclitis in combination with closer attention to bacteriaemia.

Operative treatment

Local operative procedures undertaken for the relief of secondary glaucoma are designed to assist drainage from the anterior chamber and to remove gelatinous exudate or to break ring synechiae. The simplest operation is paracentesis of the anterior chamber, which may be repeated several times if carefully done. Operations on the iris include a four-puncture iridotomy for iris bombé and a broad iridectomy for seclusio pupillae and secondary glaucoma.

(d) Choroiditis

Acute suppurative choroiditis or panophthalmitis is usually due to pyogenic infection from septic perforating wounds of the globe. The infection spreads rapidly and converts the eye into a bag of pus. The lids are swollen and oedematous, lacrimation is profuse, supra-orbital pain intense, the conjunctivae are oedematous, conjunctival and ciliary vessels are extremely congested, the cornea and aqueous are cloudy, hypopyon may be present, the lens is oedematous, and the vitreous opaque and greyish. Panophthalmitis may also occur in acute endogenous infections by metastasis, especially in pneumonia and meningitis.

Panophthalmitis

Treatment consists in excision of the eye or, in cases in which the globe has ruptured or is likely to rupture, in evisceration. Untreated cases result in phthisis bulbi. Sympathetic ophthalmitis does not occur in association with a frank panophthalmitis but may follow incomplete evisceration of an eye with retention of fragments of uveal tissue.

Treatment

Acute localized metastatic choroiditis presupposes a bacteraemia or pyaemia. The area of infection shows leucocytic infiltration and is surrounded by an area of hyperaemic reaction. In the subsequent atrophic stage there is a central pale area of absorption of choroidal tissue and of the overlying pigment epithelium of the retina, surrounded by a ring of excessive choroidal pigmentation derived from the region of reaction. In later years these choroidal pigment cells tend to migrate into the overlying retina, which is also involved in the inflammatory process.

Metastatic choroiditis

In the acute phase loss of vision, due to the presence of cells in the vitreous or of involvement of the macular area, is the main symptom and this reaches its height in a week or more. In rare instances dull supra-orbital pain may occur, but otherwise symptoms are absent. Externally the eye appears normal but ophthalmoscopy shows a haze of cells in the vitreous which may entirely obscure the details of the fundus. When the choroiditis is visible it appears as a slightly raised yellowish area with an indefinite fluffy outline. The choroiditis may be present as a single area or as numerous areas in different stages of progression (see Plate XII, D). The disease tends to pursue its course to a conclusion determined more by the local reaction in the choroid than by any form of treatment, and leaves areas of local atrophy, the position of which in the fundus governs the effect on visual acuity (see Plate XII, E). Unless the macula is involved recovery of vision is good and often complete in acute cases, but in chronic cases vitreous opacities may be permanent. Recurrent cases and those of chronic type associated with cyclitis carry a worse prognosis for vision.

*Clinical picture**Prognosis*

Miliary tuberculosis sometimes produces choroidal metastasis. The condition is seen only in the late stages of the disease after the onset of meningitis. Conglomerate tubercle of the choroid is rare and appears as a raised whitish mass projecting into the vitreous and covered by the retina. Diagnosis must be made from sarcoma of the choroid. It

Special forms of choroiditis: tuberculous

occurs in children only (Wolff). Small daughter tubercles may be seen closely clustered around the main mass. Solitary central choroiditis is usually tuberculous (Verhoeff), occurs at an early age, and is almost always unilateral. The acute stage shows a non-pigmented oedematous patch with dense vitreous opacities; in the atrophic stage there is a central atrophic patch at the posterior pole with a surrounding ring of pigmentation. Daughter foci sometimes arise close to the parent focus. The atrophic or obsolescent phase must be distinguished from familial macular coloboma (see p. 496) but is characteristically unilateral, slightly eccentric, and sometimes shows secondary foci, a familial incidence being absent. The condition is sometimes a manifestation of congenital syphilis.

Irido-cyclitis and choroiditis in a chronic relapsing form, with subacute exacerbations, may be associated with foci at the posterior pole and with perivasculitis of the retina; these cases are probably tuberculous and do not respond favourably to treatment. Disseminated choroiditis may be tuberculous, but is usually syphilitic. Pseudoglioma in prenatal life or infancy may follow diffuse tuberculosis of the choroid and retina with secondary degeneration of the vitreous. The vitreous becomes converted into an opaque greyish-yellow mass. The globe is smaller than its fellow and shows early signs of shrinking. The diagnosis is from glioma of the retina (see RETINA DISEASES, Vol. X, p. 628).

Syphilitic

Congenital syphilis presents two pictures: (i) that known as 'pepper and salt' fundus consists of numerous minute areas of pigmentation interspersed with pale or yellowish areas distributed more noticeably peripherally; (ii) disseminated choroiditis, which appears in the acute stage as small yellow fluffy patches, and in the atrophic stage as irregular patches of varying size, usually separate but sometimes confluent, scattered all over the fundus (see Plate XII, E). In old-standing cases the choroidal pigment migrates into the retina and may lie in front of the retinal vessels and cause confusion with retinitis pigmentosa (see Vol. X, p. 626) since there is also some degree of optic atrophy. Involvement of the macula seriously affects visual acuity whereas involvement of peripheral areas impairs the field of vision.

Of indefinite aetiology

Anterior choroiditis, though by some considered tuberculous, is of unknown aetiology and forms a clinical entity of importance since cyclitis often co-exists. These cases resist all forms of treatment, and the prognosis for vision is grave, particularly in cases with rheumatoid arthritis or osteoarthritis. Such cases of a quiet chronic cyclo-choroiditis may be complicated by slowly progressive optic atrophy, and finally vision may be totally lost and the vitreous be gradually filled with organization of transuded leucocytes.

Complications

The complications of choroiditis chiefly consist of extension forwards to the ciliary body and iris, and inwards to the retina and vitreous. The former have been dealt with under iritis and cyclitis (see pp. 501 and 504). Any acute choroiditis involves some change in the overlying retina if the lamina vitrea is broken, and degeneration of the retina may

become extensive. A serous exudate may cause detachment of the retina characterized by the presence of a definite vitreous haze, the absence of retinal holes, and its unsuitability for operative treatment.

Involvement of the vitreous (hyalitis) may produce permanent opacities with loss of vision, secondary cataract, vitreous abscess (endophthalmitis), or lowered tension of the eye in the stages of organization. Thus the prognosis as regards vision varies with the site of the lesion, the degree of vitreous involvement, and the incidence of complications, such as detachment of the retina, cataract, and optic atrophy. Most acute simple cases, secondary to such conditions as focal sepsis, give an excellent prognosis for vision.

Vitreous haemorrhage is easily confused with the haze from choroiditis, but the opacities are larger, more irregular in shape, and less evenly distributed in the vitreous. The age incidence of vitreous haemorrhages, except in diseases of the blood-forming organs and Eales's disease, is 55 years and onwards whereas choroiditis usually occurs between 10 and 35 years of age as an initial attack.

*Diagnosis
from vitreous
haemorrhage*

Acute retrolbulbar neuritis occurs in young adults, more often women, and rapid loss of vision is the prominent symptom. There is, however, a central scotoma, and rarely some swelling of the optic disk, but the choroid is normal and the vitreous clear. Recovery of vision is spontaneous and often complete, but some years later the full picture of disseminated sclerosis develops in most cases.

*From acute
retrolbulbar
neuritis*

Familial macular coloboma simulates solitary obsolescent macular choroiditis (see p. 496). Conglomerate tuberculosis may be confused with new growth of the choroid or retina and with Coates's disease, and old cases of atrophic disseminated choroiditis resemble retinitis pigmentosa.

*From other
conditions*

The treatment of choroiditis is that of uveitis as a whole, but the local treatment is insignificant compared with the treatment of the underlying general disease or focal sepsis. Locally acute cases are treated by rest, atropine, and heat, and many cases of unknown aetiology respond well to injections such as tuberculin and neoarsphenamine. Panophthalmitis is treated by excision or evisceration as circumstances allow, and in cases of conglomerate tubercle and phthisis bulbi the eye should be removed. In cases of pseudoglioma the eye is sometimes left for a while to assist the proper development of the orbital cavity but should ultimately be excised.

Treatment

(1)—Iris

4.—TUMOURS

Benign

1593.] Tumours of the iris include the small melanoma, a congenital spot or spots of pigment-accumulation forming a small velvety mass projecting from the anterior surface and not demanding any treatment other than periodical observation lest malignancy should develop. Angioma may be part of a wider angiomatosis, which appears as

Melanoma

Angioma

Cysts

tortuous vessels especially in the region of the two arterial circles. In rare instances there is a congenital and hereditary form of multiple cysts formed in the posterior pigmented epithelium. The commonest cyst in the iris, however, is an epithelial inclusion following perforating trauma. Leiomyoma is rare.

*Malignant**Sarcoma*

The commonest malignant tumour is a congenital mole which becomes an active sarcoma. If seen sufficiently early, excision by a broad iridectomy is often successful; later cases may require excision of the eye. Primary sarcoma of the iris stroma is rare. On the other hand the iris is not uncommonly involved in extension forwards of melanoma of the ciliary body.

(2)—Ciliary Body*Rare types**Malignant melanoma*

Fibroma, myoma, angioma, and adenoma of the ciliary epithelium have been reported but are all very rare. Malignant melanoma occurs primarily in the ciliary processes or in the choroid just behind. Extension may be forwards into the iris or the angle of the anterior chamber, backwards into the choroid and retina, or outwards through the sclera. In the anterior chamber the black streak may simulate iridodialysis but is dull to transillumination, and in the sclera a small black patch may attract attention. The growth is most often discovered during routine ophthalmoscopy when it appears as a black hemispherical mass projecting into the vitreous, and is best shown after dilatation of the pupil. Ultimately fungation into the orbit may occur. The age incidence is usually between 30 and 60 years. Glaucoma and secondary cataract are the commonest complications. The morbid anatomy, prognosis, and treatment are the same as for melanoma of the choroid.

(3)—Choroid*Benign**Plexiform neuroma
Angioma*

Plexiform neuroma is sometimes congenital and then the eye is always buphthalmic (congenital glaucoma). Angioma is also congenital and usually associated with facial naevus flammeus. The growth is broad, flat, and situated at the posterior pole. Vitreous haemorrhage and secondary glaucoma, resulting from mild trauma, draw attention to the condition. Secondary cataract supervenes in some cases.

*Malignant**Sarcoma*

Melanoma of the choroid is the commonest primary intra-ocular growth, is most often situated in the anterior half of the choroid and more rarely at the posterior pole, and appears as a dark-grey smooth rounded mass carrying the retina forward and projecting into the vitreous (see Plate XII, F). It is dull on transillumination. A small serous detachment of the retina is often seen below it. The growth consists of whorls of closely packed cells with a variable degree of overgrowth of pigment cells; large growths often show extensive degeneration. Signs

Histology

and symptoms are few. Loss of vision or metamorphopsia is due to detachment of the overlying retina, or to vitreous haemorrhages which may obscure the growth ophthalmoscopically, or to secondary cataract. Pain may occur during acute glaucoma, which is not an uncommon complication, and is often the presenting feature. Too often signs and symptoms are absent until late. Ultimately spread through the sclera, involvement of the orbit, and fungation occur with proptosis, haemorrhage, and metastases. Clinically the condition has four stages: (i) intra-ocular, which is symptomless, (ii) glaucomatous or detachment of the retina, (iii) perforating, and (iv) metastatic. Metastases, however, may occur early from involvement of the venae vorticosae. In clinical stages (i) and (ii) the prognosis after excision of the eye is generally good, and in stages (iii) and (iv) the expectation of life is about two years but much longer latency has been recorded. The differential diagnosis is from massive choroidal haemorrhage, vitreous haemorrhage, and other forms of retinal detachment.

*Signs and symptoms**Clinical stages**Prognosis**Diagnosis*

The treatment in stages (i) and (ii) is by immediate excision of the eye with as much of the optic nerve as possible. Stage (iii) demands exenteration of the orbit followed by deep X-ray therapy. If the orbital bones are not involved immediate skin grafting of the cavity should be done. In stage (iv) the only treatment is by deep X-rays and palliative measures.

Treatment

Leuco-sarcoma occurs rarely in adults and mainly in the posterior half of the choroid. It presents few signs and symptoms apart from loss of vision and metamorphopsia. The differential diagnosis is from conglomerate tuberculosis and from localized degeneration of choroid and retina such as senile exudative retinitis.

Leuco-sarcoma

Flat sarcoma occurs rarely as a pale flat mass at the posterior pole. The diagnosis is from secondary carcinoma. The treatment of the above two conditions is the same as for melanotic sarcoma.

Flat sarcoma

Metastatic carcinoma appears as a flat, yellowish, progressively enlarging mass at the posterior pole or near the optic disk. The primary tumour is most often in the breast, but occasionally in the stomach, bronchus, colon, thyroid, or uterus. Failing vision due to detachment of the retina is the sole symptom at first but later pain and glaucoma may be present. Differential diagnosis is from flat sarcoma of the choroid and retino-choroidal exudation at the posterior pole. Treatment is excision of the globe or the application of radon stitched onto or into the sclera.

Metastatic carcinoma

5.-DEGENERATIONS

1594.] Degenerations of the uveal tract affect principally the choroid. In high myopia stretching and thinning of the coats of the globe occur, confined chiefly to the posterior half and resulting in degeneration of the choroid. Areas of atrophy are seen at the posterior pole or around the disk and tend to extend slowly with the increasing myopia.

Myopic

Involvement of the macula results in posterior staphyloma, in degeneration with pigmentary disturbance, in haemorrhage, or in atrophy (see Plate XII, G). Vision becomes progressively or suddenly worse and more difficult to restore with glasses. Retinal degeneration (see Vol. X, p. 630) commonly co-exists. Drops of solution of adrenaline hydrochloride 1 in 10,000 to 1 in 6,000 twice a day may help to check the progress of the condition.

*Degenerations
of lamina
vitrea*

Degenerations of the lamina vitrea produce clearly defined yellowish patches of varied shape and size distributed in the posterior pole and around the disk. They are of uncertain, though possibly indirectly of vascular, origin, and do not require any treatment. Colloid bodies (*Drusen*) may be seen around the disk as yellow bud-like spherical excrescences of the lamina vitrea. Tay's choroiditis appears as minute, dull-yellow, punctate thickenings at the posterior pole and occur in the aged. Doyne's honeycomb choroiditis consists of yellowish-grey rounded or hexagonal areas with intervening streaks of pigmentation, is macular in distribution, and familial in incidence.

Vascular

Sclerosis of the choroidal vessels in the macular area produces an appearance of thick grey streaks accompanied by dusty pigmentation at the posterior pole. The condition is often associated with retinitis circinata (see Vol. X, p. 631) which may also be in part choroidal in origin. Hole at the macula may follow thrombosis; in the first stages a ring of oedema and haemorrhage surrounds the fovea. These undergo absorption and leave a clear punched-out hole with some surrounding pigmentary disturbance. Arteriosclerosis of retinal and choroidal vessels is constantly present.

*Retinitis
pigmentosa*

Defective choroidal circulation in the intermediate and peripheral zones is found in retinitis pigmentosa (see Vol. X, p. 626) and is held to be a contributory factor, though the essential lesion appears to be retinal. Concentrates of vitamin A given sufficiently early may be of value as a preventive.

*Choroider-
aemia*

Choroideraemia is a condition of acute atrophy of the choroid occurring in middle age and rapidly involving the whole choroid except the macular area. The condition is of unknown origin but appears to be an essential capillary atrophy. A familial incidence has been recorded. Treatment is ineffective.

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VACCINIA AND VACCINATION

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Reference may also be made to the following titles:

ENCEPHALO-MYELITIS

IMMUNITY AND IMMUNIZATION

SMALLPOX

1.-VACCINIA

1595.] Vaccinia is due to infection by the Virus vaccinia, a virus closely *Relation to*
linked to, and probably a modified form of, the virus of small-*variola*
pox, such modification, however, being all important (see SMALLPOX,

Vol. XI, p. 272). Although infection of man by the *Virus variolae* is constantly associated with a generalized pock eruption, that by the *Virus vaccinia* is almost always attended only with the production of a localized pock eruption at the site of inoculation. They vary, moreover, markedly in degree of infectivity. The *Virus variolae* can infect by aerial transmission as well as by contact; that of vaccinia infects only by actual transmission to an abraded dermal surface. The *Virus variolae* can be transformed by animal passage into the *Virus vaccinia* but the converse has never been done.

Cowpox Natural vaccinia or cowpox is now rare in England. Reece in 1921 said it was then non-existent but later in that year cases occurred in cattle and humans in Wiltshire. Isolated cases still occur; in Devonshire, in 1933, a milker was infected and four cows were found to be recovering from a recent infection.

Source of infection and transmission The source of the infection in a herd has often not been discovered, although in some cases in the past variola among humans was stated to be the cause. Transmission from cow to cow in a herd is by the hands of milkers.

Lesions in cows In milch cows the eruption occurs round and on the udders and teats. Papules proceed to vesiculation but the surrounding induration may be intense, and deep-seated ulcerations may result from the vesicles. It is stated that the rash may appear in successive crops and that lesions in varying stages of development may be present at the same time.

Lesions in man In man the initial lesions are found on the fingers and thumbs used for milking the infected cow, and infection may be spread by auto-inoculation. The type of vaccinia acquired by infection from the cow is more severe in an unvaccinated person than that occurring after vaccination with vaccine lymph.

General symptoms in man The onset is usually sudden and characterized by sore throat, high fever, headache, and prostration. This usually occurs some ten days after the inoculation. Lymphangitis and glandular swellings commonly occur. Death has apparently not been reported as following an infection. Healing may be delayed and deep ulcerations have been reported, with slow recovery. In one case reported to the Ministry of Health the rash came out in successive crops and lesions were found in different stages of development.

2.—VACCINATION

Vaccination in prevention of smallpox It is beyond the scope of this article to consider the part played by vaccination in the prevention of smallpox. It will be sufficient to quote Blaxall: 'It is recognized in all civilized countries that vaccination and revaccination at suitable intervals afford a sure protection against smallpox and that by no other means at present known can this be obtained.'

(1)—Definition

Vaccination may be defined as the operative procedure by which the *Virus vaccinia* is communicated to man.

(2)—Source of Lymph

This virus is contained in what is known as vaccine lymph, which is produced from material obtained from the lesions produced on susceptible animals, most commonly young calves, by vaccinia. The vaccinal eruption on the shaved abdominal skin of these animals is, if satisfactory in nature, scraped off and ground up with a suitable quantity of diluent. The resultant mixture is called a lymph and at the outset it contains a large number of adventitious micro-organisms. S. Mönckton Copeman in 1891 drew attention to the value of glycerin in purifying such a lymph, as at suitable temperatures it has a marked antibacterial action; its influence on the virus of vaccinia is much less marked. As a rule vaccine lymph is a mixture of vaccinal pulp (the crude vaccinal eruption) with glycerinated water with or without some preservative. Sometimes the antibacterial purification is hastened by the action of chloroform vapour or ether, for a short limited period, on the lymph. In all bacterial purification a watch must be kept that the effective potency of the lymph is not impaired. All lymphs manufactured in or imported into Great Britain and Northern Ireland must comply with the standards of purity and potency laid down by the regulations made under the Therapeutic Substances Act 1925. The potency of vaccine lymph stored at temperatures from 0° to 5° C. may be retained for three months; when stored at 5° to 10° C. the potency is retained for four weeks only; and when stored above 10° C. the potency cannot be assured beyond seven days.

*Standard of
purity*

Vaccine lymph made from vaccinal eruptions on sheep is also used.

Sheep lymph

In recent years research has proceeded on the problem of obtaining a lymph entirely free from adventitious organisms from the outset. The *Virus vaccinia* has been cultivated *in vitro* in association with living tissue-cells (embryonic chick or kidney) and on the embryonic membranes of living chicks. The results are promising but have not advanced yet to the stage of large-scale manufacture. There is also a possibility that the elementary bodies, the true virus bodies, separable by high-speed centrifugation or other means, may be utilized. These bodies, also known as Buist or Paschen bodies, are minute round coccoid bodies approximately 0.2 μ in diameter. Their specificity has been demonstrated.

*Cultivation
of virus in
vitro*

*Paschen's
elementary
bodies*

(3)—Operative Procedure

The skin at the selected site, usually on the left arm over the insertion of the deltoid muscle, is cleansed, dried, and well rubbed with alcohol which is allowed to evaporate. Vaccination on the leg cannot be recommended in the adult or the infant as there is more probability not only of severe local reaction but also of secondary infection.

*Choice and
preparation of
site*

- Technique* The ends of the capillary tube containing the lymph are broken off, and it is advisable to pass through a flame from a spirit lamp for a brief instant that end through which the lymph is to be expelled. Care must be taken not in any way to heat the lymph and the end must be allowed to cool. The other end is introduced into the rubber ejector. One or more incisions not more than $\frac{1}{4}$ inch long should be made in the long axis of the arm. These incisions (scratches or scarifications) should be so superficial that the epidermis only is penetrated and should draw no blood or only the very slightest trace of blood. Cross-scarification or hatching should not be used; it produces an unnecessary degree of injury to the skin and this may facilitate subsequent accidental contamination by micro-organisms. Its practice by public vaccinators is forbidden by the Vaccination Order of 1930. The incisions can be made either by a sharp scalpel or by a needle efficiently sterilized, for example by flaming, and allowed to cool. The lymph is driven out of the tube by slow and steady pressure on the rubber ejector. The lymph may be lightly applied by the scalpel after the incision is made or the incision may be made through a drop of the lymph previously applied. It is not advisable to rub the lymph into the wound vigorously as it is said to increase the severity of the local reaction. At every stage thorough aseptic precautions must be taken.
- Incisions*
- Application of lymph*
- After-care* The important points in the after-care are cleanliness and avoidance of mechanical injury by sleeves or shields. The lymph should be allowed to dry on the arm and, if a dressing is put on, it should be a layer of sterile gauze fastened by tapes and renewed when necessary. Crusts should be allowed to dry and fall off naturally. The vaccinated arm should be rested after the development of the papule as much as possible, especially in adults; this will lessen the local reaction. The arm in primo-vaccinates should be inspected on the seventh to tenth day and in re-vaccinates on the third or fourth day and if necessary again later. Public vaccinators are required to inspect results not earlier than the sixth day or later than the fourteenth day. The Committee on Vaccination (1928) recommended two inspections, the first from the seventh to the tenth day and the second from the fourteenth to the seventeenth day.
- Multiple pressure and drill methods* Two other methods of vaccination are recommended by the Committee on Vaccination (Ministry of Health) 1928 but we have no personal experience of them: (i) the multiple pressure method; for a full description of this consult the report by Leake, 1927; (ii) the drill method, using a sterile chisel having an edge not more than $\frac{1}{12}$ inch long which removes only a superficial epithelial cuticle.
- Number of incisions* The number of insertions or incisions must be left to the discretion of the vaccinator or of the vaccinated person or his guardian. It is the advice of the Minister of Health (1929), as conditions are at present, that in most cases one insertion will suffice, but that when maximal protection is desired, as when variola major threatens, more than one can be made up to a total of four, which should not be exceeded. In such cases the insertions should be spaced sufficiently far apart, not less than $\frac{1}{2}$ inch, to avoid the risk of the resulting vesicles coalescing. For such maximal protection three or four insertions are better than two.
- Choice of age* Primary vaccination should, by choice, be performed between the

second and sixth months after birth. It is inadvisable to vaccinate earlier than the second month although this is practised in some quarters, as such infants do not take the vaccination so well as older ones. This fact is usually ascribed to some residual transmitted maternal immunity. In any case older infants may be expected to resist better any untoward complications from without.

Children in a febrile state, or those who suffer from any irritation of the bowels or unhealthy state of the skin, particularly an eczematous condition, should not be vaccinated until their health has improved. It is important to see that the housing condition is satisfactory and, in the absence of smallpox, vaccination should be refused during the local prevalence of such infectious diseases as measles, scarlet fever, diphtheria, erysipelas, and poliomyelitis and other acute nervous ailments.

In 1929 the Minister of Health, recognizing that post-vaccinal encephalitis occurred mainly among children of school age and adults after primary vaccination, advised that it was not generally expedient at present to press for the vaccination of persons of these ages who had not been previously vaccinated unless they had been in contact with a case of smallpox or otherwise directly exposed to infection. Were there any danger of an epidemic of variola major, this precaution would have to be dispensed with in face of the graver menace.

maternal
139

*Primary
vaccination
after infancy*

(4)—Revaccination

It was suggested by the Committee on Vaccination (1928) that infantile vaccination by one insertion should be followed by revaccination on entering school (at 5 to 7 years of age) and again on leaving school (at 14 to 16 years of age). The reaction to revaccination in most of such cases may be expected to be slight. If the infantile primary vaccination has been by three or four incisions revaccination can, in our opinion, be safely deferred till the age is 10 to 12 years. This decision depends on the duration of the immunity afforded by the primary vaccination, and opinion varies on this point. By those interested the Report of the Committee on Vaccination (1928) and the Bulletins of the Office International d'Hygiène Publique (1934 and 1936) should be consulted. Some authorities believe that evidence points to the protection given by infantile vaccination persisting in some degree throughout life, but others that effective immunity lapses after a few years.

*Duration of
immunity*

(5)—The Development of Vaccinia on the Dermis

This differs according as the vaccination is primary or is a revaccination, the degree of difference depending on the amount of residual immunity in the latter. The less the immunity left in a revaccinate the closer does the course of development approximate to that of a primary vaccination.

(a) Normal Development in Primary Vaccination

The incubation period lasts about three days during which as a rule nothing is observed except in persons susceptible to trauma, when the

Incubation period

initial slight redness and oedema subside within a few hours. At the end of the third day, or on the fourth, elevated red papules surrounded by a narrow areola of hyperaemia develop along the site of the inoculation. From the fifth day a process of vesiculation begins, completed usually on the seventh day, when the shiny pocks contain a clear fluid. These, which at first are plump, become depressed in the centre, and by the ninth day become pustular. Further flattening occurs and a scab forms from the eleventh day, the colour changing from yellow to form a dark brown crust; this crust detaches itself from the sixteenth day onwards, leaving a slightly depressed scar. The areola increases until the tenth day and subsides as the pock dries up. The areola round the pock varies from $\frac{1}{4}$ inch to 2 inches in diameter and is associated with a varying amount of oedema and induration. It is a local reaction to the developing virus and with lymphs of moderate potency as a rule gives little trouble. The degree of the reaction probably varies with the susceptibility of the patient.

Constitutional symptoms

Constitutional symptoms also vary in degree. A slight rise in temperature may be noted from the third day but clinical appearances of pyrexia are not apparent till the fifth day. Usually there is some malaise concurrent with the rise in temperature and there may be some headache, backache, and pain over the splenic region and in the throat occasionally. The fever reaches its maximum on the eighth day. The abdominal pain is associated with enlargement of the spleen which occurs with some frequency and reaches its maximum usually on the eighth day. Pain in the axilla on the same side as the vaccinated arm, due to enlargement of the lymphatic glands, is common.

*Splenic enlargement**(b) Normal Development in Revaccination**'Vaccinoid' reaction*

The development and regression in a revaccination vary with the residual immunity. In persons who have been successfully vaccinated within a few years or who have had an attack of smallpox, i.e. in persons in whom there is a good residual immunity, revaccination is usually followed by redness and swelling, reaching a maximum within 48 hours, which may disappear within four days. Vesicles are rare and regression to normal takes place without scar formation. A brown stain on the skin may be the only evidence left of the revaccination. In others who have been vaccinated for the first time at a more remote date, or in whom for some reason immunity, though present, is not so pronounced, a reaction occurs which has been denoted as 'vaccinoid'. Compared to a primary vaccination, this is modified in severity, appears earlier, and runs its course within a shorter period. Vesicles may be small and aborted.

Generally in all revaccinates vesicle, pustule, and crust formation occur earlier than in primo-vaccinates. The areolar blush and oedema are also less and subside earlier. A revaccination showing papule formation with areola, or vesicle formation, may be regarded as a success and re-establishes protection against smallpox.

(6)—Abnormal Results of Vaccination

Attention will here be directed to such abnormal results as occur in practice at the present time with the use of vaccine lymph. Early textbooks are full of discussions which happily need not now be considered, such as allegations of the occurrence of post-vaccinal syphilis and tuberculosis.

(a) *Septic Infections*

In the service of the Government Lymph Establishment from 1931 to 1937 in almost one and a half million vaccinations reported upon, complaints of pyogenic inflammatory conditions such as cellulitis and septicaemia have been of the greatest rarity and in not one case was a causal part attributable to the lymph. If the vaccination is carried out in an aseptic manner and if the vaccinated person is in a healthy state and the surroundings (house and condition of other inmates) are satisfactory there should be no fear of pyogenic complications. Impetigo or other source of septic infection in other members of the family has been known to cause sepsis in the vaccinated person. Precautions must be taken to guard the vaccinal lesion from outside infection or interference.

(b) *Severe Local Reactions*

Severe local reactions resulting in an extension of the areolar blush and of the induration undoubtedly occur, but with comparative rarity, and subside from the tenth day onwards. Complaints of this nature reported by public vaccinators during three years 1934 to 1937 varied from 1 in 3,056 vaccinations to 1 in 3,244. The condition can probably be attributed to hyper-susceptibility: a parallel condition is seen in animal inoculation. It occurs more rarely in infant vaccinations and more often after the primary vaccination of adults. Evidence indicates that it occurs with greater frequency after the use of the more potent lymphs.

In some countries complaints have at times been made that, at the site of inoculation, areas of necrosis or deep ulceration with delayed healing developed. This is in our experience very rare; in fact in more than one million of reported vaccination results we can only recall one or two complaints of this nature. The freedom from such a condition in any severe degree may possibly be attributed to two causes: (i) the strain of the vaccinia virus, and (ii) the fact that most primary vaccinations in Great Britain are in infants. It may perhaps be expected that, if a large number of adults are vaccinated for the first time in the event of an epidemic, there may be an increase in the occurrence of such conditions. Apart altogether from the fact that adults take vaccinia more severely, they are more liable to such factors as trauma, contamination by dirty sleeves, and stasis of vessels due to the dependent position of the arm.

Very occasionally supernumerary vesicles appear round or near the site of inoculation; they may show immaturity in development. The condition may possibly be attributed to spread by lymphatics in cases

Incidence

*Extension of
process
Incidence*

*Necrosis and
deep
ulceration*

*Super-
numerary
vesicles*

in which it is fairly certain that there was no auto-inoculation and the skin was healthy.

*Spread by
auto-
inoculation*

Spread by auto-inoculation (scratching) can and does occur occasionally.

(c) *Rashes*

Urticarial

Erythematous

Morbilliform

Various rashes are occasionally present during the developing stage of vaccinia. An urticarial eruption may occur, usually on the first or second day. An erythematous rash is sometimes present, usually from the seventh to the tenth day in a primary vaccination. A morbilliform eruption is perhaps the most common and is usually seen from the seventh to the tenth day after vaccination. It is more copious on the limbs than on the trunk and more rarely invades the face. This differentiates it from measles.

Incidence

We believe that a rash of any severity would be reported by public vaccinators, and if this is so the incidence of such rashes may be taken to be 1 in 6,000 to 1 in 9,000 vaccinations. The analysis of complaints of local reactions and rashes received from public vaccinators in England and Wales has been made by Mr. W. Pulley of the Government Lymph Establishment. This complication, at all events in any severe form, is then also rare, as these figures were taken from an analysis of over one million recent vaccination returns. These rashes may be fairly attributed to individual susceptibility. In recent years no complaints have reached us of such severe general conditions as were formerly described under the titles of vaccinia haemorrhagica and vaccinia gangrenosa.

(d) *Generalization*

*Normal
generalization
of virus*

In every case of successful vaccination the virus is not confined to the site of inoculation but is distributed by the blood throughout the organs in varying degree. In normal vaccination, however, it does not produce any naked-eye evidence of its presence; it does not give rise to papules or vesicles, or macroscopic lesions within the internal organs.

*Abnormal
generalization*

By generalization in the clinical sense is denoted those extremely few, generally mild but in some very rare instances grave cases, in which over part or the whole of the body there is a generalized vesicular rash, and in the graver instances the patient presents the aspect of a smallpox infection. In fatal cases nodules or necrotic foci are found in internal organs. In the mildest cases a few vesicular elements occur in areas where no accidental infection from the site of inoculation can be suspected. It is not certain that some of the papular rashes may not be of this nature.

Incidence

It is, however, permissible we think to limit the term generalized vaccinia to such cases as show some vesicular rash. The rarity of such cases can be judged from the following figures: for the five years 1st July 1932 to 30th June 1937 in 1,026,588 reports of vaccinations sent in by the Public Vaccinators of England and Wales, fifteen cases and eleven doubtful cases were reported with one death, giving, if the doubtful cases are included, an incidence rate not exceeding 1 in 39,484 vaccinations and a death-rate of 1 in over 1 million. We believe that the condi-

tion is attributable to hyper-susceptibility of the vaccinated person. According to Tedder, Anders gave the following figures: 6 to 8 cases in 500,000 vaccinations (Chaveau); 4 cases in 39,915 during 1888 to 1898 and 3 cases in 170,576 during 1893 to 1897 (Haslund); 5 cases in 100,000 (Voigt); 50 to 60 in 2,285,579 (Groth).

When a generalized eruption appears in vaccinia, the constitutional disturbance accompanying it is less than in variola. Moreover the eruption appears earlier than in variola, usually between the tenth and twelfth day after inoculation. The papulo-vesicular rash has an appearance of immaturity even though some of the vesicles may become pustular. Although such an eruption appears to select the skin of the vaccinated arm more than other sites, its general distribution follows that of variola. *Comparison with variola*

(e) *Post-Vaccinal Encephalitis*

Post-vaccinal encephalitis is rare. Symptoms appear as early as the second day after vaccination and as late as the fifteenth, the mean period being ten days. The onset is usually sudden and is characterized by pyrexia, headache, vomiting, and drowsiness. Some cases are mild. Others develop paralysis which is at first spastic but which may later become flaccid. The paralysis may be localized or extensive. Convulsions may develop. Death may occur in a varying proportion of cases, from 50 per cent downwards, within two to six days. Those who recover exhibit, usually, no after-effects. Only some of the above symptoms may be present. *Clinical picture* *Mortality*

The lesions in the nervous system (Turnbull and McIntosh; Perdrau) have, as their chief characteristic, perivascular softening and demyelination. The vessels concerned are principally those of the white matter of the brain and cord. The lesions are often symmetrical. *Morbid anatomy*

The disease first became known in 1922; it affected particularly Holland and, to a less degree, Great Britain. It has been the subject of much research, in Great Britain particularly by the Andrewes Committee of 1923-5, the findings of which are embodied in the report of the Committee on Vaccination, 1928, appointed by the Minister of Health. It was found that the condition was most common after primary vaccination of children of school age and of adolescents and was exceedingly rare in infants and in cases of revaccination. *History of the disease*

Both the British Committees and the Dutch investigators agreed that the association with vaccination was not fortuitous but that vaccinia could not be held solely responsible. The nature of the association is still unknown. Most workers favour the hypothesis of the activation by vaccinia of some unknown neurotropic virus harboured, without arousing symptoms, by the vaccinees prior to vaccination. The disease was not associated with the use of lymph manufactured by any particular institute or prepared in any particular way. *Hypotheses of causation*

From December 1922 till the end of 1929, 186 cases were recorded in England and Wales with 97 deaths, or 3 cases in 100,000 vaccinations. *Incidence*

According to the Annual Reports of the Chief Medical Officer of the Ministry of Health there has been a diminution of the incidence of this disease in recent years in England and Wales. In 1934, 5 cases were reported; in 1935, no cases; in 1936, 5 cases; in 1937, 5 cases.

Greenfield considered that encephalo-myelitis following vaccination should not be regarded as a separate entity but should be grouped with forms which may follow other febrile illnesses. The lesions found in encephalitis following measles, smallpox, chicken-pox, and influenza are of the same histological nature (Perdrau and others).

Treatment

Treatment by the administration, as early as possible, of the serum of a vaccinated person (preferably recently vaccinated) or of an antivaccinal horse serum at present supplied by the Lister Institute, Elstree, Herts., may prove of use. Treatment by human serum, according to the *Further Report of the Committee on Vaccination* (1930), p. 67, was first adopted in this country by Horder (1929) on the advice of M. Gordon, and independently in Holland by Hekman. The Committee were of opinion that the cases cited by the latter supplied a powerful argument for the use of the human antivaccinal serum as a treatment which should be instituted at the earliest possible moment. The administration may be either by the intrathecal route, after allowing some cerebrospinal fluid to escape (Horder gave 5 c.c.), or by the intravenous route (reported doses 8 to 30 c.c. repeated if necessary). The relief of cerebrospinal fluid tension seems important. If human serum is used, normal precautions should be adopted to see that the donor is not syphilitic.

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VAGINA, DISEASES AND DISCHARGES

See LEUCORRHOEA AND OTHER NON-HAEMORRHAGIC VAGINAL
DISCHARGES, Vol. VII, p. 710; *and* VULVA AND VAGINA
DISEASES, p. 606

VARICOCELE

See VEIN DISEASES, p. 532

VARICOSE VEINS

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VASOVAGAL SYNCOPE

See BRAIN: VASCULAR DISORDERS, Vol. II, p. 642

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VEIN DISEASES

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Reference may also be made to the following titles:

ANEURYSM	THROMBOSIS OF CEREBRAL
ANGIOMA	VEINS AND SINUSES

1.-ANATOMICAL CONSIDERATIONS

*Venous
circulation*

1596.] The veins form a system of thin-walled vessels conveying the blood from the peripheral capillary plexuses in the tissues to the heart. The circulation of the blood in the veins is maintained partly by differences in the blood-pressure, which is highest in the small veins at the periphery and lowest in the large veins near the heart, partly by the movement of the body tissues established by muscular action, and partly, in the systemic circulation, by a series of cusp-like valves which prevent regurgitation of the blood, that might occur in the limbs as the result of either the action of gravity or a sudden increase in the blood-pressure in the great veins near the heart.

*Histology of
walls*

The vein wall of the smallest vessels consists merely of a single layer of endothelium. As the vessels become larger this is reinforced with an outer support of connective tissue, which in the larger veins is supplemented by elastic tissue and in the venae cavae by a certain

amount of unstriped muscular tissue; this, in the inferior vena cava, possesses the same power of rhythmic contractility as does the muscle of the right auricle of the heart with which it has a common developmental origin in the sinus venosus.

It is customary to divide the veins into four systems according to *Systems* their collective areas of distribution: namely, pulmonary, cerebral, portal, and systemic. The pulmonary venous system collects the *Pulmonary* oxygenated blood from the capillary plexuses among the alveoli of the lungs and delivers it into the left auricle of the heart through the pulmonary veins. The veins throughout are very thin-walled for their size and are without valves.

The cerebral veins consist of a vast network of endothelial tubes *Cerebral* which receive not only the arterial blood from the cerebral tissues but also a certain proportion of the cerebrospinal fluid. They discharge into the great venous sinuses of the brain and thence through various foramina in the skull into the jugular veins and other superficial veins of the head and neck. Owing to their thin walls and poor external support they are particularly liable to bleed severely as the result of trauma of the skull and are the chief source of intracranial haemorrhage in cases of fractured skull or concussion. These veins are also without valves.

The veins of the portal system convey to the liver the products of *Portal* digestion as well as the water absorbed from the large intestine. They collect the blood from the capillaries throughout the intestinal tract and converge via the mesenteric veins to the portal veins of the transverse fissures of the liver. Just before entering the liver the splenic vein inosculates with this system. The portal vein breaks up into a mass of capillaries among the cells of the liver and the blood, from which the bulk of the food-products is removed, is collected into another capillary system whence it is conveyed through the hepatic vein into the inferior vena cava and so to the right auricle. The veins are valveless and any increase of blood-pressure is reflected to the lowest branches around the anus and rectum, which become distended to form haemorrhoids or piles. (See also Vol. VIII, p. 91, and Vol. X, p. 503.)

The systemic circulation returns the blood from the limbs, trunk, *Systemic* head, and neck through a system of veins, some of which are situated deeply among the muscles and others superficially in the deeper layers of the fatty subcutaneous tissue where they form a network visible to the naked eye except in very obese subjects. The smaller veins accompany the peripheral arteries and are usually two or three in number, intercommunicating freely and known as *venae comites*. The larger veins formed by the confluence of the *venae comites* and other vessels run independently but in nearly all cases alongside of the corresponding arteries and ultimately converge, from the head, neck, and upper extremities into the superior vena cava and from the lower extremities and portal system into the inferior vena cava, whence the

venous blood is poured into the right auricle of the heart to be propelled through the right ventricle and pulmonary artery into the venous plexuses of the pulmonary system.

Valves

Arranged throughout the veins of the systemic circulation are a series of bicuspid and tricuspid valves, usually situated in the neighbourhood of venous junctions. They are particularly common in the extremities where sudden increase of venous pressure from intra-abdominal or intrathoracic pressure and also the action of gravity against which the blood-stream is flowing have to be overcome. These valves act by the falling together of the cusps and obliteration of the lumen of the veins, thus preventing the reflux of blood beyond the valve. They may be seen in the superficial veins forming a series of knot-like thickenings on coughing or exertion. Under certain conditions of stretching or inflammation of the vein wall or endothelium these cusps fail to meet and the valve then becomes incompetent and fails in its purpose of stopping the venous reflux—a condition commonly met in advanced cases of varicose veins and detected clinically by the presence of a reflex thrill down the whole course of the affected vein when the patient coughs or strains.

Relation to lymphatics

The veins of all these systems are closely accompanied throughout their course by the lymphatic vessels draining the corresponding areas, and for this reason the groups of lymphatic glands are generally situated in the neighbourhood of important venous junctions such as in the groin, axilla, and root of the neck. This anatomical fact must be taken into account when dealing surgically with such affections of the lymph nodes as abscesses and explains the venous dilatation from congestion which is so common in conditions of enlarged lymph nodes, as for example mediastinal glands in cases of Hodgkin's disease.

2.—OBSTRUCTION

Compensatory enlargement of minor veins follows an obliteration of any large vein resulting from either injury or inflammation. There is temporary embarrassment of the circulation in the limb, shown by cyanosis and pitting oedema of the part beyond the obstruction. This condition improves as a compensatory circulation is established by enlargement and development of other venous channels. This re-establishment of the circulation can be hastened by judicious active movement and massage which should be begun as early as possible after the obliteration. Where superficial veins are enlarged they become obvious as distended and tortuous vessels, the valves of which tend to become incompetent from the resultant stretching of their walls. They are, however, lined with normal endothelium and must not be mistaken for varicose veins, though in the course of time degenerative changes in their walls convert them into varicose veins.

It is important in the early stages to realize these differences as

obliteration of these compensatory channels often causes permanent oedema of the limb and a lasting embarrassment of the circulation. Though surgical interference may be justifiable and necessary in the late stages when valvular incompetence has become permanently established, in the early stages all that is called for is massage and an elastic support, such as a suitable stocking or crêpe bandage, which will enable the patient to get about without discomfort or swelling of the part while the circulation has a chance to become re-established, when the dilated superficial vessels will permanently return to normal.

3.—VARICOSE VEINS

This condition is undoubtedly hereditary and its incidence seems to follow the Mendelian law. The expression varicose veins usually denotes a dilated and tortuous condition of the systemic veins but varicosities occur in the portal circulation and haemorrhoids and varicose veins are often associated in the same person. As might be expected, gravity and the upright position render varicose veins far more noticeable in the lower extremities, and it is seldom that they are complained of elsewhere though undoubtedly the changes about to be described in the walls of the veins can be detected in vessels elsewhere in the body. *Inheritance*

The changes in the walls of varicose veins consist in an absence of elastic tissues and degeneration in the endothelial lining, with considerable perivascular fibrosis which increases with time so that the vessels become tortuous and dilated with rigid and thickened walls as the result of the dilatation. Irregular distension of the veins occurs in certain situations. The cusp-like valves become incompetent and allow reflux of venous blood on exercise with undue venous-pressure in the lower parts of the limb, the tissues of which consequently become cyanotic with impaired nutrition and therefore liable to infection and ulceration on very slight provocation. As the result of increased tension aching pain is often present, and the impaired circulation often results in pitting oedema at the periphery of the limb. *Changes in walls and valves*

These varicose conditions of the veins start in, and exist primarily in, the deeper veins of the muscles and bones of the limb and it is not until communications between the deep and superficial veins become affected and their valves incompetent that superficial varices become apparent; varicose veins therefore are not usually noticed until adult life or until the strain of prolonged standing or pregnancy causes prolonged and undue pressure on the venous system of the lower limbs. The connecting veins between the superficial and deep systems of the lower limbs are situated at the saphenous opening, at the junction of the lower and middle thirds of the thigh, in the popliteal space, and at the junction of the upper and middle and lower and middle thirds of the leg on the inner side. The superficial varices

become manifest at these points in the first place, and are a most marked formation frequently observed as prominent masses of dilated veins.

*Localized
varicosities
caused by
trauma*

Undoubtedly in a few cases local trauma with its subsequent inflammatory reaction leads to the development of a localized patch of varicose veins at some part of the limb, but these seldom spread or increase greatly unless there is a family history of varicose veins.

*Examination
of patient
to determine
condition of
veins*

A patient with varicose veins, especially if they are of the great saphenous type, must be carefully examined to ascertain whether a reflex thrill is present on coughing, indicating that valvular incompetence is already present. Moreover, if such a thrill is present in the upper part of the great saphenous vein it must next be ascertained, by obliterating this vein in the middle of the thigh and again making the patient cough, if such a thrill can be detected below the communicating vein in the lower part of the thigh. If this is present, which it not uncommonly is in old-standing cases, it indicates that this communicating vein as well as that at the saphenous opening needs surgical attention. In only a very few cases can a thrill be detected below the knee when the saphenous vein is obliterated at that level, but its presence necessitates surgical intervention for obliteration of the vein below the communication in the upper part of the leg. It is important to be certain of the presence of valvular incompetence before deciding on the appropriate treatment.

*Choice of
treatment*

The modern treatment of varicose veins by obliteration of the lumen of the vessel by aseptic thrombosis produced by injection of some mild irritant is more than unlikely to be successful in the presence of valvular incompetence with reflux of blood. In cases in which a thrill can be detected it is advisable, and in the opinion of most surgeons necessary, to obliterate the veins at one or more places by ligation before success by injection treatment can be expected.

*Injection
treatment*

The injection treatment of varicose veins consists in the introduction into the lumen of the vein of some mildly irritant substance which will produce not only thrombosis of the stagnant blood but irritation and granulation of the damaged endothelial lining with consequent fibrosis, narrowing, and obliteration of the lumen of the vein. Many substances have been used for this purpose and many techniques employed; the treatment has now been in use for approximately twenty years and has stood the test of time; its results are uniformly satisfactory if the method is employed in suitable cases and it has the advantage of allowing the patient to continue his vocation throughout the treatment. The risk of detachment of clot is extremely small but it does rarely occur and a few fatal cases have been reported. The results immediately lead, as has been stated, to obliteration of the venous circulation in that area and a compensatory enlargement of surrounding veins, so that a certain number of patients return for a recurrence; if all cases are carefully followed up it will be found that some 30 per cent of patients return in from one to five years for further

injections in these locally enlarged compensatory veins—injections which can be carried out with confidence and success. This rapid and aseptic thrombosis is produced more easily in varicose than in normal veins. By each injection several inches of vein can be obliterated and in cases which are not very extensive a course of several injections will produce great benefit.

There appears to be no risk of embolism so long as the resulting thrombus remains sterile, but it is an additional safeguard to make the injection with the patient sitting up and the leg straight out or hanging down, according to which position enables the vein to be just visible, as when the patient is erect the blood in a varicose vein flows toward the periphery. *Embolism*

Many solutions have been used for injection, all of which will effect a cure provided the fluid is injected *into* the vein and none escapes into the tissues around, an accident often resulting in sloughing of the tissues and ulceration. The following solutions can be used; all must, of course, be sterile: sodium salicylate, 20 to 40 per cent solution, 1 to 3 c.c. for each injection; sodium morrhuate, 5 per cent solution, 5 c.c.; sodium chloride, 20 per cent solution, 3 to 10 c.c.; dextrose, 50 per cent solution, 5 c.c.; mercuric chloride, 1 or 2 per cent solution, 1 to 3 c.c.; quinine hydrochloride, 5 per cent with urethane, 2.5 per cent in saline, 5 to 15 c.c.; or quinine hydrochloride 9 per cent solution, with 4.5 per cent of urethane, 1 to 5 c.c. After considerable experience, the quinine and urethane solution is recommended, usually a 5 per cent solution of quinine hydrochloride with 5 c.c. as the initial injection, the 9 per cent quinine solution being given only in those rare cases in which the 5 per cent solution fails to produce thrombosis. The injection is painless though some stiffness and discoloration occur locally in twenty-four hours, and the general effects are slight and transitory; the reaction continues locally for about ten days and no second injection should be given *anywhere* until all tenderness on palpation has gone from the thrombosed area, usually fourteen days after the first injection. *Solutions used*

It is impossible to give a prognosis as to the results; in some patients the entire leg is cured by one injection, in others clotting occurs only for an inch or so; some veins clot completely and in others a small central canal persists with a thickened wall, so that the vein no longer bulges or shows. *Choice of solution*

Certain cases are unsuitable for injection, e.g. (i) deep femoral thrombosis and white leg, (ii) the acute phlebitis which often follows injury, (iii) pregnancy, as other veins appear subsequently and there may be a risk of abortion, and (iv) the presence of a Trendelenburg back-impulse on coughing; such cases *never* clot unless Trendelenburg's operation for the ligation of the saphenous vein is first carried out. *Results*

The patient sits with the leg either straight out or dependent so that the vein just shows. The leg is then cleaned with 2 per cent solution of iodine in alcohol. Care must be taken to ensure that the needle is in the lumen of the *Contra-indications*

Technique

vein, by withdrawing some blood into the syringe. The injection in all cases should be made from above downwards starting with the highest group of veins and 5 c.c. of quinine and urethane solution injected into one or more selected sites; the injected veins should then be firmly stroked a few times from the point of injection towards the periphery; this ensures a more extensive obliteration. A sponge is held over the puncture and a piece of zinc oxide plaster applied, or if the veins are large they should be bandaged to prevent a mass of clotted veins forming. The patient can then walk away and pursue his usual avocation.

Trendelenburg's operation

Whenever there is a thrill or impulse on coughing, and especially when the varicose veins are confined to the great saphenous system and are causing pain from back pressure, Trendelenburg's operation should be performed, and this is essential as a preliminary to injection in all cases in which such a thrill is present on coughing.

Technique

This consists in ligation of the great saphenous vein and removal of a portion of it as high up as possible, and it is best to excise completely the saphenous pouch and the branches which enter it. By this means the back pressure from the big veins of the trunk is cut off. An incision two inches long should be made a finger's breadth internal to the femoral pulse over the saphenous opening and running downwards and outwards. Through this the vein and its branches are isolated and tied in two places and portions of them are removed. Four separate branches will usually be found entering the saphenous pouch. Injection of the veins below can be carried out at the time of operation and subsequently during the patient's convalescence.

Injection in presence of eczema and ulceration

The presence of varicose eczema or ulceration in the lower part of the limb does not contra-indicate treatment by injection, though it may be difficult to ascertain the position of the veins above this area owing to oedema. In such cases it is well to apply a varicosan or elasto-plast bandage for a fortnight, and when it is removed the reduction in the oedema will enable the veins to be visualized so that they can be easily injected, a procedure which is rapidly followed by amelioration in varicose eczema and healing of ulceration.

4.-VARICOCELE

Aetiology

The aetiology of the varicose condition of the veins of the pampiniform plexus known as varicocele is often obscure though its more common presence on the left side of the body suggests that the right-angled opening of the left spermatic vein into the renal vein renders its radicles more liable to obstruction than the sloping opening of the right spermatic vein into the inferior vena cava. The condition is undoubtedly aggravated in constipated individuals by the drag of the loaded sigmoid colon and rectum compressing and distorting the left spermatic vein as it crosses the pelvic brim just behind the pelvi-rectal junction.

Constipation

New growth of kidney

Varicocele may be secondary to new growths of either kidney which obstruct the venous return into the renal vein, or to carcinoma of the pelvi-rectal region causing similar congestion, and more rarely retro-

peritoneal teratomas or sarcomas may cause varicosity of one or both pampiniform plexuses. If a varicocele occurs on the right side it is probably due to a right renal growth. In every case therefore, especially when the onset of the varicocele is sudden, the urine should be examined for blood and the abdomen palpated carefully. Should one of these primary causes be discovered it obviously calls for urgent treatment, if possible by removal, when the secondary scrotal condition will improve.

In most cases, however, unilateral varicocele, usually left-sided, exists without any obvious cause, even constipation being absent, and in these cases it cannot be too strongly urged that no treatment is called for unless the condition is causing pain and discomfort. Unless the patient's attention is directed to it and his mind disturbed by unfounded tales of the danger of impotence if the condition is left untreated, he is rarely troubled by its presence. *Idiopathic cases*

Clinically the condition is easily recognized. It is usually unilateral and left-sided and the distorted, tortuous, and distended veins give a typical appearance, often likened to 'a bag of worms' within the pendulous scrotum. The patients are often young, anaemic, and neurotic and complain of intense pain in the testis, abnormal sexual feelings, impotence, or asthenia. The testis is often smaller than the one on the opposite side and a small hydrocele may be present. Careful rectal and abdominal examination must be made to exclude the possibility of any organic lesion elsewhere, and the heart should be examined. *Clinical picture*

In some few cases, especially in hot countries and in patients taking riding exercise, if the scrotum is pendulous, pain and a congested feeling result from exertion; in these circumstances, as also in candidates for the services in whom a varicocele may be used as a cause of malinger-*Indications for treatment*ing, it is justifiable to interfere.

In elderly patients all that is usually necessary is a well fitted net suspensory bandage to support the scrotum against the perineum; this need be worn only during the day and is a source of comfort to the patient. Suspensory bandages are not recommended for neurotic young men as their presence tends to concentrate the patient's attention on his genitalia. In cases in which a suspensory bandage is ill tolerated, or in which the patient is a candidate for one of the services, operation may be undertaken and the main mass of the pampiniform plexus ligated. Recently the injection of quinine and similar drugs has been successful in clotting the veins; but this treatment must be used with caution as some cases of sloughing of the cord have followed escape of the fluid into the connective tissues. *Suspender*
Operation
Injection

5.—WOUNDS

Contusions of veins result in most cases in aseptic phlebitis, but this may be converted into a septic phlebitis from infection transmitted *Contusion*

through the damaged overlying skin tissues. The treatment of these conditions is dealt with subsequently but is essentially rest. For the contusion, cold compresses or a dressing damped with evaporating lead lotion should be applied over the bruised area.

*Incised and
punctured
wounds*

Incised or punctured wounds of veins may result from accident, deliberate injury, or occur during venesection. Haemorrhage in a steady stream of more or less severity results, according to the size of the vein affected. Partial severance of a vessel is often followed by bleeding which will cease if the vessel is completely cut across. The blood emerges in a steady stream and is at first dark in colour but rapidly becomes oxygenated on exposure to the air. Except in the case of wounds of large veins, venous haemorrhage is seldom fatal as it is rapidly controlled; occasionally, especially in the case of wounds of the large veins at the base of the neck, air is sucked into the vein, and if this occurs in any great amount sudden death may occur from cardiac embarrassment following a churning of the air in the heart cavities.

*Treatment of
venous
haemorrhage*

The treatment of venous haemorrhage is pressure distal to the wound, elevation of the part above the heart level, and application of a pad and bandage over the wound. Subsequent debridement of the wound with ligature of the damaged vessel must be carried out under aseptic precautions and a general anaesthetic is usually required. When it is suspected that air is being sucked into the wound a wet pad soaked with sterile fluid, e.g. saline, should be placed over the puncture immediately. The haemorrhage from ruptured varicose veins in the leg when the valves are incompetent is often alarming and occasionally fatal unless prompt treatment is carried out on the lines indicated.

*Arteriovenous
aneurysm*

As a result of perforating wounds of veins, either by venesection or accident, a communication may be established with neighbouring arteries and an arteriovenous aneurysm result. Injuries of this nature were particularly common after gun-shot wounds in the war 1914-18; they give rise to a pulsatile tumour below which a tortuous and often pulsating vein can be detected though it may be masked by oedema of the limb. On auscultation over the tumour a characteristic buzzing bruit can be heard. In the acute stages considerable and sudden collapse may result from the sudden loss of a large quantity of blood from the circulation into the over-distended veins of the affected limb. When following a fracture of the anterior fossa of the skull behind the orbit this condition gives rise to one form of pulsating exophthalmos. (See also ENOPHTHALMOS AND EXOPHTHALMOS, Vol. V, p. 47.) Treatment consists in ligature of both artery and vein above and below the tumour with, if possible, excision of the sac, except in the case of the post-orbital arteriovenous aneurysm when ligature of the internal carotid artery is the only treatment possible—an operation which is fraught with some risk of hemiplegia.

6.—PHLEBITIS

The formation of a clot in a vein usually follows trauma sufficiently severe to damage the wall of the vein without causing its rupture; should rupture occur escape of blood takes place into the tissues and a bruise results from the extensive extravascular clotting. Aseptic *Aseptic* phlebitis with the formation of a hard, localized, and adherent clot may be produced either by a blow or by an injection of sclerosing fluids into veins, the endothelial lining of which is degenerate or damaged, a similar trauma or injection producing little or no reaction in a normal vein. Septic phlebitis results from trauma and infection *Septic* and follows transmission of organisms through the damaged skin; this is particularly liable to occur with impaired nutrition of the tissues arising with varicosity of the underlying veins. The condition also follows childbirth or abdominal operations when infection has occurred. In these cases the iliac or femoral veins are commonly affected with resulting persistent and painful oedema of the leg—a condition known as ‘white leg’ (phlegmasia alba dolens), which pro- *‘White leg’* duces considerable disability and discomfort which is usually permanent. (See also PUERPERIUM, Vol. X, p. 392.) In either case there is a hard painful swelling on the course of the vein over the thrombosed area, and bruising and discoloration appear in the surrounding tissues. In septic phlebitis suppuration may rarely ensue.

In septic phlebitis there is a danger that portions of the loose clot may be detached and carried into the circulation where they become arrested in the capillary plexuses, often in the lungs, giving rise to pyaemic abscesses the advent of which is heralded by rigors. In extreme cases pulmonary embolism may result in the rapid death of a patient or, more favourably, produce a pulmonary lesion with consolidation from which it will take a considerable time to recover. (See also LUNG DISEASES: POST-OPERATIVE COMPLICATIONS, Vol. VIII, p. 241.) *Complication of septic phlebitis*

Aseptic phlebitis calls for no further treatment than for a few days’ rest with the limb elevated, after which, as with injection of veins, the patient can resume his normal occupation, care being taken that further trauma is not incurred. Should oedema persist light massage is often beneficial. *Treatment of aseptic phlebitis*

Septic phlebitis calls for more cautious treatment as clot is liable to be detached. The patient should be confined to bed with the limb elevated and if necessary slung for two to three weeks, i.e. until the temperature has been settled for at least seven days. After this the patient may be allowed to use the limb cautiously, if necessary with a crêpe bandage support, but massage should be avoided for at least six weeks. Any primary focus of infection must be sought and treated adequately, but not until the venous thrombosis has subsided. *Of septic phlebitis*

Thrombophlebitis migrans

This is an interesting and distressing condition of obscure aetiology, manifested by the appearance of recurrent thromboses in the superficial and deep veins all about the body; they are thought to be connected with some infective focus but this is often hard to find and may be impossible to demonstrate; but such sources as septic tonsils, infected nasal sinuses, chronically inflamed gall-bladder or appendix, and pyorrhoea alveolaris should be eradicated if definitely present, though operation in these cases is attended with a very definite risk of pulmonary embolism and spread of thrombosis. A similar condition occurs in cases in which, immediately after ligation of the saphenous vein, injections of varicose veins are carried out; not uncommonly this is ultimately fatal, so that it is unwise to perform these two operations at one sitting. The illness may last many months and is tedious and very debilitating but, except when the thrombosis affects deep veins in vital situations, is seldom fatal though persistent oedema of the limb, consequent on deep thromboses, may persist for several weeks after the patient has been convalescent.

Treatment

Treatment consists in rest in bed, but it is unwise to attempt to remove infective foci in the acute stage of the disease because of the risk of embolism mentioned above, and as a general rule no operation to this end should be undertaken for at least two months from the onset of the disease.

Local treatment is that for thrombosis and phlebitis and consists essentially in the application of cooling lotions. As a general rule sulphanilamide is contra-indicated, as most of these cases appear to be staphylococcal in origin; if tried it must be used very cautiously and abandoned at once if no fall in temperature and general improvement result within thirty-six hours.

7.-TUMOURS

*Sarcoma,
endothelioma,
and
perithelioma*

Tumours of veins are rare. Sarcoma and endothelioma are occasionally reported as beginning in the lining of the larger vessels but are seldom diagnosed and are of merely pathological interest. Endothelioma and perithelioma occur round the smaller vessels and must be regarded merely as a mildly malignant sarcomatous neoplasm which is seldom diagnosed except on microscopy after removal.

*Haem-
angiomas*

Haemangiomas are not uncommon and vary from spider-like capillary telangiectases to cavernous haemangiomas containing large spaces which may affect the entire limb. Not infrequently they communicate with the arterioles, and if this communication is free it may cause a pulsating cirroid aneurysm. These cavernous haemangiomas may be associated with the formation of a considerable amount of fibro-fatty tissue in and around the distended venous spaces, and the skin over

them is sometimes markedly pigmented (naevus). The tumours are usually bluish and easily diagnosed.

Treatment of capillary haemangiomas consists of the application of solid carbon dioxide or of radium or other means to promote coagulation. That of cavernous haemangiomas consists of excision if possible, injection of boiling water into the vessels to procure obliteration, or injection of one of the sclerosing fluids already enumerated the result of which, however, is often disappointing as the endothelial lining of these tumours is normal. (See also Vol. I, p. 578.)

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VELDT SORE

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1.—DEFINITION

(*Synonyms*.—Barcoo rot; Natal sore; septic sore; desert sore; gifseer; brandseer; dermatitis veldis)

1597.] The name veldt sore has been given to an extremely chronic shallow punched-out ulcer occurring in the arms or legs of Europeans settling in tropical or semitropical countries. Its shallowness distinguishes it from tropical sore which invades deeply, and it differs from the common skin lesions in its extreme chronicity and resistance to treatment.

2.—HISTORY

It has long been observed that when Europeans settle in hot, dry, tropical or semitropical climates, they not uncommonly develop on their face, arms, or legs chronic punched-out ulcers which resist all forms of treatment. Various names have not surprisingly crept into the literature dealing with these, as shown by the list of synonyms given above.

The term veldt sore was first used by English settlers in South Africa many years before the Boer War. At the same time the Boers or Afrikaner farmers, suffering equally from these strange superficial ulcers,

*In South
Africa*

referred to them as gifseer (poison-ulcer) or brandseer (burning ulcer). When the British soldiers campaigning in South Africa during the Boer War developed these ulcers in noticeable numbers, descriptions and discussions of this unusual lesion began to appear in the English journals (Pridmore; Austen; Ogston; Harland; Guise-Moores; Berne; Harman; Purdy; and Dolbey).

Harman suggested that the veldt sore of South Africa was indistinguishable from a chronic ulcer found among bushmen of the Barcoo River, North Queensland, Australia. His suggestion was strongly supported by Australian soldiers who claimed that the sores they suffered from while resident in the Barcoo River country were identical with the veldt sores they developed when campaigning in the African veldt. For this reason and for want of better evidence, Barcoo rot and veldt sore are regarded as synonymous.

*Similar
disease in
Australia*

Medical men in the field under war conditions in 1900 had poor facilities for scientific investigation. A praiseworthy effort by Ogston in 1901 is, however, of interest. He made smears from the floors of chronic ulcers and from the contents of vesicles in the early stage on some clean fragments of glass, preserved them carefully, and eventually found the smears to contain a 'small bacterium growing in pairs' which he named *Micrococcus campeneus*. Subsequent research, however, failed to corroborate this finding. In 1902-3 Harman, after much research, concluded that the causal organism was *Staphylococcus aureus*, a view which has also since failed to receive support.

*Early
bacterio-
logical
investigations*

During the War 1914-18 attention was again focused on veldt sore. Troops serving in Mesopotamia developed superficial chronic ulcers in large numbers, and again the Australians recognized the similarity between these ulcers and Barcoo rot. Martin, with better bacteriological facilities and knowledge than was available during the Boer War, now found cocci and diphtheroid bacilli in both the early and late stages of the lesion but failed to realize the importance of the diphtheria. Walshe in 1918, while investigating diphtheritic paralysis, noted the coincidence of an epidemic of 'septic sores' and an epidemic of mild faucial diphtheria, and Craig in 1919 investigated veldt sores with this in mind. He succeeded in showing the similarity, if not identity, between the Klebs-Loeffler bacillus and the bacillus found in scrapings from veldt sores and from hair follicles in their neighbourhood and also demonstrated the healing properties of antidiphtheritic serum when applied to these ulcers.

*Observations
during War
1914-18*

*Recognition
of diphtheroid
bacilli*

Since the publication of Craig's work, active interest in veldt sore seems to have waned and letters from practitioners in all parts of South Africa and Rhodesia are unanimous in the view that veldt sore is not nearly such a scourge as it once was and that in many regions it has disappeared. Cases still occur, particularly in dry sandy parts, but the incidence of the disease is on the wane. Many cases occur in the ill-nourished and somewhat unwashed members of the poorer classes settled in subtropical districts.

*Present
diminution of
the disease*

3.—AETIOLOGY

Geographical distribution According to Manson-Bahr, veldt sore is found in all tropical or sub-tropical countries where desert conditions exist, e.g. Australia, South Africa, Mesopotamia, Equatorial Africa, Egypt, the Sudan, Gallipoli, and Palestine. Description of ulcers not unlike veldt sore have come from medical men working in India (Murison), the Federated Malay States (Orme), and, during the Great War, the Sudan.

Bacteriology The cause of this condition remains a matter for debate. That the *C. diphtheriae* is the sole cause can hardly be accepted in view of the peculiar tropical and subtropical distribution of the disease. The suggestion that some other factor, such as a dietetic deficiency, may be necessary cannot be lightly set aside when the difficulties of supplying a sufficiency of fruit and vegetables in hot dry climates are remembered. The Indians and the native races (Bantu) resident in South Africa appear to be exempt (Harman), and it is noteworthy that faucial diphtheria also is rare among the Bantu. Dolbey pointed out that veldt sore appeared among the troops only after they had been resident in South Africa for three months or more, a point in favour of the need for a food deficiency to develop before susceptibility set in. Dolbey also pointed out that dark-haired individuals were least susceptible, fair-haired moderately so, and red-haired most of all. Mounted units usually suffered more than the infantry, and those mounted on camels showed the highest incidence. According to Pridmore, officers suffered conspicuously less than the men, a further point in favour of some dietetic factor as a cause. Various writers, however, are not agreed upon this point, nor is there consensus of opinion upon the part played by various bacteria, insects, and animal parasites. Ticks, lice, mosquitoes, and house-flies have all been blamed, but the evidence put forward is meagre.

Other possible factors

Harman, Dolbey, and Martin agreed upon the part played by diet. When diet is restricted, the sores flourish; when large quantities of lime-juice and a good all-round diet are given, they rapidly clear up. Harland, however, found veldt sores among healthy persons living under most favourable conditions. Purdy considered that sunlight exerted a deleterious effect upon the sores and advised their protection from this agent.

It would seem therefore that veldt sore cannot be ascribed to any single or simple cause. There are probably two or three causal factors including *C. diphtheriae*, a food deficiency factor, and some inherent constitutional factor that goes with red hair and not with black.

4.—MORBID ANATOMY

Site

The ulcers tend to occur on exposed parts covered by hair, e.g. the dorsum of the hands, the forearms, elbows, knees, face, eyebrows, cheeks, and ears. They may follow slight trauma or arise spontaneously

in the neighbourhood of a hair follicle. Most intractable are those on the hands.

In the earliest stages there is a small fresh unopened blister within the layers of the epidermis. When this attains about half an inch in diameter it bursts, giving rise to a chronic ulcer in the base of which can be found the deeper layers of the epidermis. The dermis beneath the floor of the ulcer is invaded by leucocytes. Organisms are present in the intercellular spaces of the epidermis surrounding the ulcer. The shallow ulcer left after the blister has burst may spread peripherally and the final diameter varies from less than half an inch to two inches or more. The typical ulcer has a punched-out appearance with indurated edges; the base may be covered with a grey scaly debris or give rise to a muco-purulent exudate of varying amount. This variation in the dryness of the base has given rise to the suggestion that there may be two types of sore, the one found on the Lowveldt (Natal) differing from that of the Highveldt (Transvaal). Indeed, the sore found in Natal is sometimes accompanied by a frank discharge of pus and may result in abscess formation. The typical sore has a dryish base which suggests a pearly-grey membrane and is exquisitely sensitive. The edges become indurated with the appearance of cyanosis and give the sore a punched-out appearance. Occasionally ulcers may have ragged and irregular edges. The ulcer may persist for months or even years. Healing gives rise to thin paper-like scars which persist for many years and tend to be naked of hairs or sweat-glands. The ulcers are usually single but may be multiple.

5.—CLINICAL PICTURE AND COMPLICATIONS

The blister is usually accompanied by a sensation of pricking, burning, or itching. Hence the Boer term 'brandseer' (burning sore). In most cases the sore is accompanied by very little constitutional change or other evidence of impaired health. The regional lymph glands may show reaction and enlargement, especially when there is wide-spread secondary streptococcal or staphylococcal infection; but even in uncomplicated cases fever, malaise, and headache may occur.

Walshe pointed out that these sores may be followed or accompanied by all the various forms of paralysis associated with faucial diphtheria, from local paralysis, i.e. of the muscles of the involved limb, to paralysis of the muscles of accommodation and of the soft palate, or, in extreme cases, generalized peripheral neuritis with loss of all reflexes and anaesthesia. Indeed, in advanced cases the picture closely resembles that of beri-beri or locomotor ataxy. In one series of 30 patients 27 per cent showed local paralysis, 33 per cent showed paralysis of accommodation, and all showed polyneuritis in varying degrees. In 6 of these cases the sores were single and in 24 multiple. In most of them the nervous lesions developed after the sore had healed.

In Mesopotamia during the Great War, according to some observers,

Perinephric abscess

perinephric abscess was a common and serious complication. Presumably the not-infrequent infection by staphylococci had a bearing upon this development, and it must not be forgotten that several of the earlier writers regarded the staphylococcus as mainly responsible for the sore.

6.—DIFFERENTIAL DIAGNOSIS

Diagnosis from tropical ulcer

Another chronic ulcer occurring mainly on the legs and arms in tropical and subtropical countries, namely, tropical ulcer, must not be confused with veldt sore. Tropical ulcer occurs in the non-European races, particularly of Africa and Assam, and seldom attacks the white races; the depth and obvious sloughing nature of the lesion renders differentiation from veldt sore easy.

From Barcoo rot

Some writers state that there is a difference between Barcoo rot and veldt sore in that the former not uncommonly develops a firmly adherent thick hard crust. It seems probable, however, that the name Barcoo rot has been applied somewhat loosely to many forms of chronic superficial cutaneous ulceration, and little purpose is served by distinguishing between the two conditions.

7.—TREATMENT

Local protection

In districts where veldt sore is endemic, it is a useful precaution to protect the legs and arms against avoidable abrasions. Short trousers on mounted men should be forbidden and care should be taken to avoid contact with dried or moist horse manure which is known to harbour the diphtheria bacillus. All superficial injuries should be treated immediately with antiseptic lotions and kept clean.

Serum

Local application of antiseptics has long proved disappointing. Injection of diphtheria antitoxin, 4,000 units, subcutaneously in the neighbourhood of the sores, aided by the application of lint soaked in serum direct to the ulcer, seems to be much the best treatment and yields the most dramatic results in chronic cases. Especial care should be paid to diet and all vitamins must be included on a liberal scale.

Diet

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VENTRICULOGRAPHY

See RADIOLOGY IN DIAGNOSIS AND TREATMENT, Vol. X, p. 466

VERRUCA

NECROGENICA: See HAND, DISEASES AND DEFORMITIES, Vol. VI, p. 195; and SKIN DISEASES: TUMOURS, Vol. XI, p. 194
PEDIS: See FOOT, DISEASES AND DEFORMITIES, Vol. V, p. 433
PERUVIANA: See BARTONELLOSIS, Vol. II, p. 298

VERSION

See LABOUR, Vol. VII, pp. 472, 480, and 545

VERTIGO

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Reference may also be made to the following titles:

CRANIAL NERVE	DEAFNESS
AFFECTIONS	EAR DISEASES

1.—DEFINITION

(*Synonym.*—Giddiness)

1598.] Vertigo or giddiness is a 'disordered condition in which the person affected has a sense of whirling, either of external objects or of himself, and tends to lose equilibrium' (Oxford English Dictionary).

2.—AETIOLOGY

The balancing mechanism Vertigo is caused by disturbance of the balancing mechanism which comprises (i) the vestibular part of the labyrinth, i.e. the three semi-circular canals, the otoliths in the saccule and utricle, with the vestibular part of the eighth nerve and the associated tracts in the mid-brain, cerebellum, and cerebrum; (ii) the eyes and optic tracts; and (iii) the sensory nerves of the muscles, joints, and tendons, especially those of the neck.

Types of vertigo Several types of vertigo are recognized. (i) Vertigo due to abnormalities of the labyrinth or its tracts is the commonest of all.

(ii) Vertigo may be due to abnormalities of other end-organs, e.g. visual giddiness and giddiness caused by fibrositis or other lesions of the neck muscles which affect the neck reflexes of equilibrium. Visual giddiness can often be produced in a normal person by watching a

waterfall or by disturbing the field of vision by placing a prism lens before one eye.

(iii) Vertigo may be due to interference with nerve tracts other than the vestibular, e.g. in *tabes dorsalis*, *Friedreich's ataxy*, and *disseminated sclerosis*.

(iv) Vertigo due to intracranial conditions is often essentially labyrinthine; for example, rise of intracranial pressure may prevent the excretion of the labyrinth fluids and cause a choked labyrinth in exactly the same way as it does a choked optic disk. A tumour or cyst of the cerebello-pontine angle compresses the eighth nerve. Lesions of the mid-brain may affect the supranuclear tracts. Cerebellar lesions cause giddiness independently of the labyrinth. Injuries to the skull are often followed by giddiness, sometimes due to direct injury to the labyrinth; sometimes, apparently, to alterations of pressure within the cranial cavity, as, for example, after a large decompression. *Intracranial causes*

(v) Toxic vertigo is produced by drugs, such as tobacco, alcohol, and quinine, and probably by some general infections. Alcohol acts centrally, quinine probably on the nerve-endings. Suppuration in the paranasal sinuses causes giddiness, which may be due to postnasal irritation and subsequent obstruction of the Eustachian tubes as well as to toxic absorption. *Toxins*

(vi) Low and high blood-pressures are often associated with vertigo, but the immediate cause is probably labyrinthine anaemia or congestion respectively. *Blood-pressure*

(vii) Vertigo is common in epilepsy, especially in *petit mal*. 'Laryngeal vertigo' is probably due to temporary asphyxia. Vertigo is frequent in epidemic encephalitis, the lesion being usually in the nuclei. The 'epidemic vertigo' of Gerlier was probably due to encephalitis. Vertigo occurs in congenital and acquired syphilis but is not common; in congenital syphilis there is degeneration of the nerve-endings and, later, of the ganglia; in acquired syphilis the lesion is either a neuro-meningitis in the late secondary stage or, rarely, a gumma. Epidemic cerebrospinal meningitis may cause vertigo by invasion of the labyrinth from within the cranial cavity through the internal auditory meatus; if this happens, the labyrinth is usually completely destroyed, and giddiness soon ceases, as the intact labyrinth of the opposite side assumes control. *Infections*

(viii) It is very doubtful if there is a true 'neurasthenic vertigo', i.e. a giddiness without any organic basis. It is not surprising that sufferers from vertigo often become neurasthenic, a severe attack of giddiness being a terrifying experience, and the ever present fear of such an attack in traffic or at work shattering the patient's confidence. The neurasthenia is primarily a result, not a cause; once established, however, it becomes an important contributory factor. Similarly, there is no 'gastric vertigo'; the 'bilious attacks' which often accompany giddiness are the effect, not the cause, of labyrinthine irritation. But victims of seasickness are well aware of the disastrous results of dietary indiscretion or constipation before sailing, and the explanation may be that *'Neurasthenic vertigo'*

accumulation of intestinal toxins makes the labyrinth more sensitive. (See also TRAVEL-SICKNESS, p. 224.)

*Double
causation*

This last consideration raises an important point. Two factors, neither alone strong enough to cause giddiness, may do so when working together. It is known, for instance, that irritation of the trigeminal nerve can increase the irritability of the vestibular nerve and so lower the threshold of stimulation; thus giddiness and tinnitus can be produced by an impacted wisdom tooth. Sometimes vertigo, due apparently to a trivial Eustachian obstruction, does not cease until an error of refraction or a fibrositis of the neck has been treated.

3.—LABYRINTHINE OR AURAL VERTIGO

(1)—Physiology and Anatomy

Aural vertigo

Labyrinthine disturbance is by far the commonest cause of vertigo and all forms of giddiness of this nature are here described as aural vertigo. This is not merely a matter of convenience, for the essential mechanism of all kinds of vertigo due to labyrinthine disturbance is the same—inequality of activity between the labyrinths of the two sides. Normally the labyrinth is in a state of tonic stimulation and sends a continuous stream of impulses to the higher centres. So long as the activity of the two sides is equal, vertigo does not occur, however much the activity is increased or diminished; but as soon as there is any sudden inequality of activity between the two sides vertigo is experienced. For example, if one ear is syringed with water a few degrees below normal body-temperature intense giddiness is caused; but not if both ears are syringed simultaneously, although the labyrinthine irritation may be great enough to produce strong reflex movements. The power of compensation in the labyrinth mechanism is very great. If one labyrinth is completely destroyed the surviving labyrinth assumes control, and in a few weeks giddiness ceases. Compensation for sudden fluctuations of activity is far less perfect.

*Structure of
the labyrinth*

In order fully to understand the causes of labyrinthine vertigo it is necessary to review very briefly a few points in the structure of the labyrinth (see Fig. 48). The bony labyrinth lies in the petrous bone and consists of the semicircular canals, the vestibule, and the cochlea. It is filled with fluid, the perilymph, in which floats the membranous labyrinth, filled with endolymph and containing the sensory receptors, the organ of Corti in the cochlea, the cristae in the ampullae of the three semicircular canals, and the maculae of the saccule and utricle. These end-organs consist of hair-cells attached to an overlying membrane (the cupulae of the cristae and the otolith membrane of the maculae).

*Labyrinthine
mechanism*

The most plausible explanation of the labyrinthine mechanism is that the stimulus for the cristae is a movement of endolymph which shifts the cupulae and so pulls on the hair-cells; the stimulus for the maculae is a displacement of the otolith membranes by gravity and again a pull on the hair-cells. For the labyrinths of the two sides to be in a state of equal activity the endolymph pressure must be the same in each. Any

difference of pressure between the two labyrinths will cause a difference in activity, and vertigo will occur.

(2)—Factors Influencing Intra-Labyrinthine Pressure

The intra-labyrinthine pressure can be altered by factors either outside or inside the labyrinth.

(i) Factors outside the labyrinth. The outer bony wall of the labyrinth is the inner wall of the middle ear, which is perforated by the fenestra *Extra-labyrinthine factors*

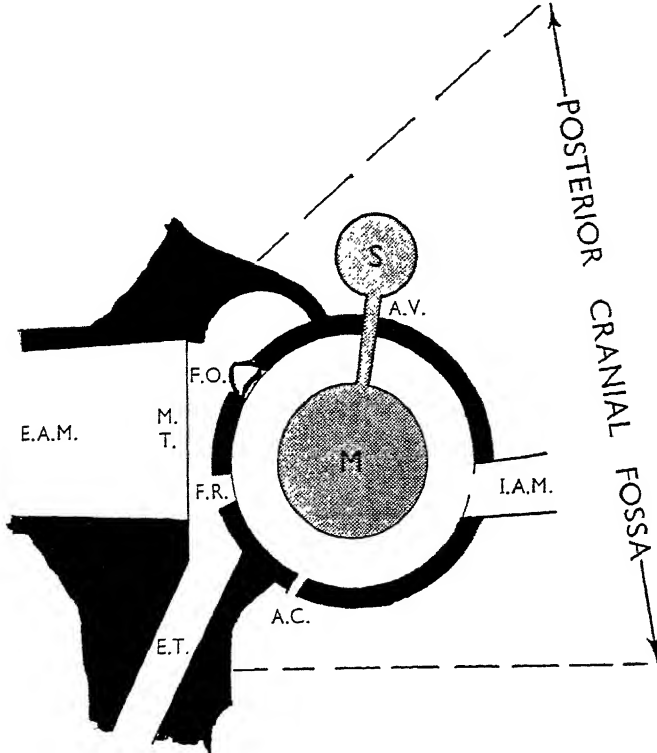


FIG. 48.—Diagram showing relations of perilymph and endolymph systems to the middle ear and cranial cavity (endolymph system cross-hatched). E.A.M., external auditory meatus; I.A.M., internal auditory meatus; M.T., membrana tympani; E.T., Eustachian tube; F.O., fenestra ovalis with stapes; F.R., fenestra rotunda; A.C., aqueduct of cochlea; M, membranous labyrinth communicating by the ductus endolymphaticus with S, the saccus endolymphaticus; and A.V., aqueduct of the vestibule

rotunda (fenestra cochleae) and the fenestra ovalis (fenestra vestibuli), in which the stapes lies. Interference with either fenestra may affect the pressure within the labyrinth. Another extra-labyrinthine factor may be obstruction to the exit of the labyrinthine fluids. The perilymph communicates freely with the cerebrospinal fluid through the aqueduct of the perilymph (aqueduct of the cochlea), which opens into the posterior fossa at the edge of the jugular foramen, and along the pia-arachnoid sheath of the eighth nerve. Thus increased pressure in the posterior fossa raises the pressure of the perilymph. The endolymph escapes from

Interference with fenestra

Obstruction of fluids

the membranous labyrinth through the wall of the saccus endolymphaticus, which lies outside the bony labyrinth between the two coats of the dura of the cerebellum and communicates with the main system of the membranous labyrinth through the ductus endolymphaticus.

Intra-labyrinthine factors
Classification of types

(ii) Factors within the labyrinth. These include alterations in the volume of the blood or of the labyrinthine fluids.

It is convenient to recognize two main clinical groups of cases of aural vertigo; those due to suppuration in the middle ear, and those without suppuration. The distinction between these groups is vital; in aural suppuration vertigo is a symptom of a condition which may at any time become dangerous to life, whereas aural giddiness, however distressing, without suppuration is never dangerous.

(3)—Aural Vertigo with Middle-Ear Suppuration

This must always be regarded with the gravest suspicion, as it may indicate the presence of a cerebellar abscess or the onset of labyrinthitis (see EAR DISEASES, Vol. IV, p. 421). Three principal forms of labyrinthitis are recognized.

Labyrinthitis circumscripta

(i) In labyrinthitis circumscripta or labyrinthine fistula there is an erosion of the wall of the bony labyrinth, usually over the bulge of the external semicircular canal near the aditus of the mastoid antrum. This erosion, by exposing the endosteum of the canal, makes it possible for pressure from without to be transmitted directly to the perilymph and so to the endolymph. Thus pressure of a finger on the tragus raises the pressure in the external auditory meatus and middle ear and affects the endolymph with the result that violent nystagmus and vertigo occur. This is the so-called fistula sign. Strictly speaking, there is no true fistula, as the lumen of the bony canal is still separated from the middle-ear cavities by the endosteum.

Fistula sign

Serous labyrinthitis

(ii) Serous labyrinthitis is an inflammation of the labyrinth associated with middle-ear suppuration but without direct invasion. It may fairly be compared to the 'sympathetic' effusion into a joint which often follows periarticular inflammation. The giddiness is first due to irritation of the affected labyrinth by the increase of pressure due to effusion, and perhaps to spread of toxins from the suppuration without, and in the later stages, when the affected labyrinth is depressed by the advance of the condition, to overaction of the unaffected labyrinth of the other side.

Suppurative labyrinthitis

(iii) Suppurative labyrinthitis is due to direct spread of suppuration into the labyrinth and is characterized by the prostrating violence of the vertigo. The stage of irritation lasts only a few hours, often less, before the nerve-endings are completely destroyed, and then giddiness is due to the unbalanced action of the labyrinth on the unaffected side and continues until compensation is complete.

Vertigo may be caused by the pressure of effusion in the middle ear on the fenestrae or by granulations in these regions. In many such cases there is erosion of the labyrinth wall, and a transient vascular congestion may be the determining factor.

In all cases in which vertigo accompanies suppuration the treatment is that of the suppurative condition.

(4)—Aural Vertigo without Suppuration

In a description of aural vertigo without suppuration Ménière's syndrome must be considered. Recently an attempt has been made to distinguish between the syndrome and the disease. Dandy suggested that the term Ménière's disease should be used for intractable cases of vertigo which he regards as due to an affection of the vestibular nerve, but there seems to be no pathological justification for this distinction. *Ménière's syndrome*

The condition is best defined as a sudden alteration in the activity of the eighth nerve in its auditory and vestibular portions (de Kleyn). Thus the condition is characterized by sudden giddiness associated with changes in hearing, usually tinnitus and deafness, in recurrent attacks. Ménière believed that this was due to a haemorrhage into the labyrinth and based his opinion on the post-mortem appearances found in the one fatal case in his series. This was long before the days of pathological histology, and the diagnosis is made more obscure by the fact that he published two different accounts of his findings. One thing, however, is certain; labyrinthine haemorrhage cannot cause repeated attacks of vertigo. In the rare cases of leukaemia with labyrinthine haemorrhage the labyrinth is destroyed. There is one violent attack which gradually passes off, and then the labyrinth of the opposite side takes control and vertigo ceases. It may be some weeks before compensation is complete, but once this has happened there are not any more attacks. *Labyrinthine haemorrhage*

The term 'Ménière's syndrome' covers such a multiplicity of causal conditions that it should be abandoned in spite of its historical associations. The symptom-group can be produced by any factor which can cause a sudden change of pressure in the labyrinth or by toxic agents.

The simplest cause of aural vertigo is cerumen. A plug of cerumen in the external meatus is suddenly pushed in against the drum, perhaps by the pressure of a finger on the tragus when the patient is shaving. The drum carries the ossicles in with it and the stapes is pushed into the oval fenestra. This raises the pressure in the labyrinth on the affected side and causes immediate giddiness. In much the same way obstruction of the Eustachian tubes can cause vertigo, the mechanism being as follows. When the tube is blocked, the air in the middle ear is absorbed, and the drum is forced in by the atmospheric pressure in the meatus, carrying the ossicles with it. This usually happens slowly, and there is plenty of time for compensation between the labyrinths of the two sides, but they are in a state of compensated imbalance. If there is now any sudden change of pressure, however slight, in either Eustachian tube, such as the shifting of a bubble of mucus, giddiness follows immediately. This is probably the commonest cause of aural vertigo. *Cerumen*
Eustachian obstruction

Circulatory conditions cause vertigo by alteration of the blood-supply to the labyrinth or perhaps to the supra-labyrinthine tracts. The commonest circulatory cause is inadequate blood-pressure. Many *Blood-pressure*

patients with high blood-pressure suffer from vertigo, which is too often regarded as a direct result of the high tension. Disastrously successful efforts are made to reduce the tension, and the patient is giddier than ever. Careful inquiry then shows that the attacks come on when the diastolic pressure is lowered to a point inadequate for the patient's needs.

*Lermoyez's
vertigo*

A peculiar kind of circulatory vertigo has been described by Lermoyez as 'the giddiness which makes one hear'. This condition is probably caused by a spasm of the labyrinthine arterioles, with anaemia and deafness. When the spasm passes, the vessels dilate, and the patient hears again, but the sudden dilatation causes a rush of blood to the labyrinth, with disturbance of intra-labyrinthine pressure and vertigo. The fact that this kind of vertigo has been noted in patients with Raynaud's disease supports this explanation.

(5)—Diagnosis and Treatment

Disease of the central nervous system, errors of refraction, syphilis, over-indulgence in alcohol or tobacco, and suppuration of the middle ear should be excluded. The history is seldom of much help, but it must be decided whether there is genuine vertigo, as patients sometimes speak of giddiness or dizziness when they mean a transitory feeling of faintness, tinnitus, or even the scintillating scotoma of a migraine. Vertigo coming on after a hot bath, after violent purgation, or on jumping out of bed, is probably due, partially at any rate, to circulatory conditions. Vertigo preceded by 'stuffiness' in one ear is nearly always due to Eustachian obstruction. Vertigo accompanied by a sensation of 'falling forward into a pit' is said to be associated with suppuration in the paranasal sinuses. The direction of apparent movement is usually uncertain, but the direction of falling, if it can be ascertained, is important. In true labyrinthine vertigo the fall is always away from the more active labyrinth. Thus when a labyrinth is irritated the fall is towards the normal side; when a labyrinth is depressed or destroyed the fall is away from the normal side. Examination of hearing may show little change unless the patient is seen during an attack, but the audiometer and tuning-forks will always show some abnormality, although possibly very small. In the later stages of the disease there is steady deterioration of hearing on the affected side, gradually advancing to complete deafness. Examination of the labyrinth during quiet periods rarely shows any abnormality which can be detected by present methods until the condition is far advanced. During an attack there are usually nystagmus and a 'pointing error', but the patient's distress precludes full examination.

*Direction of
apparent
movement*

Hearing

*Eustachian
tubes*

It is absolutely essential to be sure that both Eustachian tubes are patent, for there may be obstruction on the side with the better hearing. It is not enough for the patient to say that he 'feels the ears click' when he tries to inflate the middle ears by Valsalva's method; we must *see* the drums move, and if there is any doubt at all an Eustachian catheter must be passed. Whether there is tubal obstruction or not, the nose and

nasopharynx must be carefully examined for sinus suppuration, and the teeth and tonsils for local sepsis. *Nose and mouth*

Vertigo is not uncommon in otosclerosis, but it is transient and seldom severe enough to give much trouble. It is probably due to sudden circulatory changes in the newly-formed bone. *Otosclerosis*

When all these possibilities have been excluded, there is left a group of cases which have been ascribed to an increase in the volume of labyrinthine fluid, a 'glaucoma' of the labyrinth. This could be caused by obstruction to the escape of endolymph from the saccus (Portmann); angio-neurotic oedema (Quincke); some allergic condition (Dohlman); or intracellular labyrinth oedema (Mygind and Dederling). According to Mygind and Dederling this oedema is caused by a generalized water-retention; Eustachian obstruction in these cases is not a causal factor but is a result of the general condition, and the gradual deterioration of the labyrinth is due to continued excessive pressure of fluid on the nerve-endings. *Oedema*

Recently a most important advance has been made in our knowledge of this condition. Hallpike and Cairns have described their findings in two patients who died after an operation for the relief of Ménière's syndrome. In both cases there was a general dilatation of the whole endolymph system on the affected side. This might be due to many possible causes, such as those mentioned above; there is another possibility, suggested by Wright, that in this group of cases we are dealing with a focal labyrinthitis, caused by sepsis elsewhere in the body. In support of his view he has produced an extensive series of cases in which Ménière's syndrome was cured by the elimination of septic foci. *Septic foci*

Mygind and Dederling's treatment is to diminish fluid intake to the physiological minimum aided by a salt-free diet, with massage and light treatment to increase elimination. Furstenberg, Lashmet, and Lathrop, following the lines laid down by Mygind, found that additional sodium chloride in the diet increased fluid retention; in fact, an increase of sodium salts could bring on an attack of giddiness even when fluid was restricted. They found also that if ammonium chloride was given in increasing doses fluid intake could be increased with safety. They advise the following diet: (i) proteins unrestricted or forced; (ii) calorie content as needed for the patient; (iii) 45 grains of ammonium chloride with each meal, three days on and two days off; (iv) water intake unrestricted, but excess should be avoided; (v) low salt content—salted meat and fish, salt butter, oysters, and cheese to be avoided. *Diet*

When these measures fail or are inapplicable one of three things can be done: (i) an attempt can be made to relieve pressure in the labyrinth by establishing a fistula on the external canal (Peters) or by draining the saccus endolymphaticus (Portmann), operations which have been successful in some cases but are only suitable for the small group of cases in which there is good hearing with intractable giddiness; (ii) the labyrinth can be destroyed either by exposing and opening the vestibule or, more simply, by exposing the external semicircular canal, opening *Operation*

it, and injecting alcohol; the cases, fortunately uncommon, in which intractable giddiness follows an otherwise successful radical mastoid operation with a healed and healthy cavity are best treated in this way; (iii) the eighth nerve can be divided, as advised by Dandy, who found it possible to divide the vestibular branch without injuring the auditory branch. This operation, which necessitates a large decompression, is much more severe than alcohol injection and has not yet been proved to be more efficacious.

Finally, in the treatment of vertigo it must always be borne in mind that there may be a double causation, a factor which predisposes by lowering the threshold of stimulation and a factor which brings on the attack. It is most important to reassure the patient. He can be told with absolute confidence that he is suffering from a 'real' physical condition, not from 'nerves', and that his condition is ultimately curable. Bulbocapnine and, to a lesser degree, chlorbutol appear to have some specific action on the labyrinth, and some patients are relieved by minute doses of phenobarbitone, but hypnotics and sedatives must be used with the greatest caution; as a rule tonics are more needed. It is only in the rare cases in which all other methods fail that surgical intervention need be considered.

Drugs

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VESICANT GASES

See GASSING AND POISON GASES IN WAR, Vol. V, p. 503

VESICULITIS

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Reference may also be made to the following titles:

EPIDIDYMITIS

GONORRHOEA

1.—DEFINITION AND AETIOLOGY

1599.] Vesiculitis (sometimes called spermato-cystitis), or inflammation of the seminal vesicles, may be either acute or chronic and is almost invariably secondary to an infection of the urethra. It is a common complication of gonorrhoea, but the infection may be due to other bacteria, such as *Bact. coli*, staphylococcus, or streptococcus.

2.—MORBID ANATOMY

The wall of the vesicle is greatly thickened, and its mucous membrane swollen and congested. Since vesiculitis is often complicated by occlusion of the ejaculatory ducts, the secretion is retained and is mixed with

epithelial debris, spermatozoa, and pus cells. Usually the amount of pus retained in a vesicle is moderate, and an empyema of that organ is uncommon. When the infection becomes chronic, fibrous thickening of the wall takes place, and perivesiculitis is commonly present.

3.—ACUTE VESICULITIS

(1)—Clinical Picture

Symptoms of acute vesiculitis are usually obscured by those of the acute infection of the prostate and prostatic urethra, of which the vesiculitis is a sequel. An attack of acute epididymitis is a common complication, due to the spread of organisms along the vas. If the acute infection of the vesicle occurs during the course of a gonorrhoea, the patient will complain of urgent and frequent micturition, perineal pain, and frequent and painful erections. The erections are often followed by painful emissions, the ejaculated seminal fluid being stained dark brown with altered blood pigment. Pain is commonly complained of, not only in the perineum but also in the region of the sacro-iliac synchondroses, the groin, and the testicles. During defaecation the pain is intensified through the pressure exerted on the distended vesicles.

(2)—Diagnosis

Diagnosis rests on the above-mentioned symptoms and on the discovery, by rectal palpation, of a tender swelling in the region of the vesicle. The vesiculitis is almost invariably associated with a prostatitis, and therefore with pus in the urine and in the expressed prostatic and vesicular secretions.

(3)—Treatment

In the acute stage, any active local treatment of the urethral infection, such as irrigation, must be suspended, and treatment confined to the administration of diuretics and analgesics. Recently, the use of one of the sulphanilamide preparations has been found of great value in the treatment of vesiculitis, whether it is due to infection with the gonococcus or whether to other organisms. Rest in bed is of paramount importance, not only on account of the vesiculitis, but also as a means of reducing the risks of a descending infection along the cord. The bowels must be kept open, and pain relieved by hot rectal douches or diathermy. When severe, a suppository containing morphine $\frac{1}{4}$ grain and extract belladonna $\frac{1}{4}$ grain should be used night and morning.

Sulph-anilamide

4.—CHRONIC VESICULITIS

This may be a sequel to an acute attack, or a complication of chronic infection of the prostatic urethra.

(1)—Clinical Picture

The symptoms may be conveniently subdivided into sexual and nervous. The sexual symptoms, as in the acute cases, are frequent erections, and emissions containing pus and pigmented brown from the presence of degenerated blood. The nervous symptoms are pain, depression, and lassitude. In old-standing cases, the patients may become neurasthenic, their attention being entirely concentrated on their sex organs and their days spent in recording their symptoms and in bewailing the loss of their sexual health. *Spermatorrhoea*, i.e. the escape by day of seminal fluid containing spermatozoa and other elements, without erection or desire, may be noticeable and may confirm the patient in his opinion that his sexual capacity has been irretrievably lost.

(2)—Diagnosis

Sometimes the local symptoms are so slight and the neurasthenia so well developed that the existence of a vesiculitis is overlooked. It should therefore be an invariable rule to make a careful rectal examination of the prostate and vesicles in all patients complaining of the symptoms above described. Not only must any signs of induration of the vesicles be carefully sought for, but also the sensibility of the vesicles on the two sides compared. Finally, prostatic and vesicular fluid must be expressed by gentle massage and examined under the microscope for the presence of pus cells.

(3)—Treatment

This consists in the treatment of the primary urethral infection, to which the vesiculitis is secondary, as well as in direct treatment of the inflamed vesicle. Amongst the measures adopted to combat the urethral infection the most important is the use of the Janet method of irrigating the posterior urethra and bladder, in order to reduce surface infection. Of the measures directed to the vesicle, the most important is attention to its drainage. Emptying the vesicle of its retained secretions is effected by careful massage, with the patient in the knee-elbow position. This should be done after distending the bladder with solution, so that the infected material massaged out of the vesicle may be expelled at the end of the treatment by getting the patient to empty his bladder. Massage should be carried out two or three times a week until examination of the expressed fluid shows that it contains only two or three pus cells per microscopic field.

Supplementary methods of treatment are rectal irrigation with hot water, or, better still, diathermy with rectal and suprapubic electrodes. Diathermy may conveniently be given prior to the massage, and often it will be found that the preliminary heating of the vesicle increases the amount of secretion subsequently expelled from it by massage.

Efforts to empty the vesicle by means of massage sometimes prove

Operative treatment

ineffective because of the ejaculatory ducts being blocked. In these cases, drainage can only be effected either by catheterization of the ducts or by incision of the infected glands. Catheterization can sometimes be carried out with comparative ease through a posterior urethroscope, but in other cases the openings of the ejaculatory ducts into the posterior urethra are so placed that it is mechanically impossible.

Open operation

In these circumstances the only means of draining the vesicle is by open operation. Three types of operation may be carried out, Belfield's operation, vesiculotomy, and vesiculectomy.

Belfield's operation consists of exposing the vas at the neck of the scrotum, puncturing it with a sterile needle, and injecting medicated fluid into the prostatic section of the vas, ampulla, and vesicle. Using a silver salt, Belfield was able to demonstrate by means of radiographs that it was possible in this way to fill the vesicle completely with antiseptic fluid. Opinion is divided as to the value of his procedure, some authorities, such as F. Kidd, reporting highly of it, and others, including the writer, regarding it of doubtful value.

Vesiculotomy and vesiculectomy

Drainage or excision of the inflamed vesicle by open operation is a difficult and serious undertaking and is only exceptionally justified, when the infected gland is a source of general ill-health or the primary focus of a crippling gonorrhoeal rheumatism. Four approaches are available: the perineal, the suprapubic, the inguinal, and the transvesical.

Perineal approach

In the perineal approach, the vesicles are exposed through a curved pre-rectal incision such as is used in perineal prostatectomy. The patient having been placed in the lithotomy position with a cushion under the sacrum, the posterior surface of the prostate is exposed as for a perineal prostatectomy. By careful dissection, the base of the prostate and the vesicles are separated from the rectum. Great assistance in this operation is rendered by the use of a Young's prostatic retractor, which allows the prostate and vesicles to be dragged down into the perineal wound and avoids the necessity of working in the depths of a cavity. The fascia over the seminal vesicles is then incised, the remaining steps in the operation depending on whether vesiculotomy or vesiculectomy is to be carried out. In the former procedure, all that is necessary is to incise the inflamed vesicle, insert a drainage tube, and bring the skin together with sutures. If the vesicle is to be excised, it must be separated from the prostate and base of the bladder by careful dissection, special care being necessary at the outer extremity, which is in close relation to the prostatovesicular venous plexus, and the point of entry of its main blood-supply.

Suprapubic vesiculectomy

In suprapubic vesiculectomy, the vesicle is approached through a median suprapubic incision, similar to that employed in approaching the lowest portion of the ureter. The peritoneum is separated backwards, and the bladder is pushed upwards and forwards until the seminal vesicles are found lying deeply in the pelvis.

Inguinal approach

The inguinal approach is similar to the suprapubic, except for the fact that the incision is oblique, resembling that used in the removal of a ureteric calculus impacted at the brim of the pelvis.

Transvesical approach

Probably the easiest approach to a surgeon unaccustomed to perineal prostatectomy is through the bladder base, employing the technique devised by Thomson-Walker in 1924. With the patient in the Trendelenburg position,

the bladder is exposed and opened, as in the operation for open prostatectomy. An incision is then made in the floor of the bladder, extending from the posterior lip of the internal meatus backwards in the middle line for two and a half inches. This incision cuts through the bladder mucous membrane, the trigonal muscle, and the muscle of the bladder wall immediately behind it. Through this bladder wound the vesicles are exposed and may be excised with comparative ease. Afterwards the edges of the median bladder incision are brought together with fine catgut sutures, a small tube being inserted so as to drain the cavity behind the bladder. The bladder is then closed and drained as after a suprapubic prostatectomy, the tube in the retrovesical space being brought out of the abdominal wall in company with the suprapubic catheter.

5.—TUBERCULOSIS OF THE SEMINAL VESICLES

In genital tuberculosis, the seminal vesicle is seldom affected alone, a *Aetiology* tuberculous vesiculitis being found in association with tuberculosis of the epididymis and of the prostate. Whether in such cases the vesicular infection is primary and the epididymal secondary, or vice versa, is still a matter of controversy.

Usually the symptoms are slight, and the lesion is only discovered *Clinical picture* during the routine examination of a patient who is found to be suffering from a tuberculous epididymitis. When symptoms exist they are similar to those described in the previous paragraph, namely, sexual irritation with painful and blood-stained emissions. Rectal examination reveals the presence of a nodular tender vesicle, with a hard craggy outline, and marked peri-vesicular induration. On cystoscopy the bladder is found to be normal or, if it has become infected from the vesicle, it shows the presence of tuberculous lesions immediately behind the base of the trigone.

Only rarely is vesiculectomy indicated. As a rule, treatment is confined *Treatment* to dealing with the tuberculous infection of the epididymis, followed by the adoption of the general constitutional remedies employed for a tuberculous infection occurring anywhere in the body. It will usually be found that the removal of the tuberculous epididymis or testicle has an immediate beneficial effect on the infected vesicle, and few operators have followed Young in the heroic surgical procedure he advocates of total excision of the seminal tract. In the opinion of most surgeons, even a vesiculotomy is comparatively rarely indicated in the treatment of genital tuberculosis. When it is undertaken, either of the four routes of exposure may be employed.

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VINCENT'S ANGINA

See PHARYNX DISEASES, Vol. IX, p. 574

VIRCHOW'S DISEASE

See BONE DISEASES, Vol. II, p. 566

VIRILISM

See ADRENAL GLAND DISEASES, Vol. I, p. 247

VISCEROPTOSIS

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Reference may also be made to the following title:

KIDNEY, SURGICAL DISEASES

1.—DEFINITION

(*Synonyms*.—Enteroptosis; splachnoptosis; Glénard's disease)

1600.] Visceroptosis is often defined as a condition in which the abdominal viscera are situated at an abnormally low level in the abdominal cavity. The weakness of such a definition is that careful radiological studies of the position of such organs as the stomach and colon, which can be readily visualized, show that these organs occupy no fixed position in healthy persons. It is thus impossible to define any particular position as abnormal. Moreover, there is no real evidence that variations in the anatomical position of such organs as the stomach and colon produce any constant clinical syndrome. Although a large number of variable symptoms may be associated with a low position of the abdominal viscera, there is no proof that the ptosis is the cause of the symptoms, and it is more probable that both the ptosis and the symptoms may be due to a common underlying cause.

2.—AETIOLOGY

Before the advent of radiology it was usually assumed that the abdominal viscera occupied more or less fixed positions; but in 1885 Glénard *Glénard's hypothesis* showed that organs such as the colon, stomach, liver, and kidney were

often found to lie at a lower level in the abdomen than was considered normal. He attributed certain local and general symptoms, such as abdominal discomfort, flatulence, exhaustion, and neurasthenia, to ptosis of the abdominal viscera, especially of the colon. In his conception the ptosis produced kinking and angulation of the intestines, which led to stasis of their contents with absorption of toxins. Later he modified his purely mechanical explanation of ptosis by assuming a functional derangement of the liver which, according to his view, produced a diminution in the muscular tone of the intestine.

Normal positions of stomach and colon

The introduction of X-ray examination of the intestinal tract shed much light on visceroptosis. Moody, van Nuys, and Chamberlain attempted to determine accurately the position of the stomach and colon in young healthy persons who had not suffered from any dyspeptic symptoms. Their radiological investigations showed that when examined in the erect position the greater curvature of the stomach dropped below the inter-iliac line, i.e. a line drawn between the highest points on the iliac crests, in 74 per cent of men and 87 per cent of women; further, in 25 per cent of the men and 46 per cent of the women it was more than three inches below this line. Moreover, they showed in both men and women that in the recumbent position the stomach rose to a much higher position. Later Moody investigated the position of the stomach in patients over forty years of age complaining of gastric symptoms and found that a low position of the stomach occurred more often in healthy young adults than in these elderly dyspeptics.

Mobility of abdominal viscera

Barclay, from a series of radiological studies, has come to the conclusion that one of the most striking features of the abdominal viscera is their mobility, and has said: 'The normal abdominal viscera have no fixed shapes and no fixed positions, and every description of them must be qualified by a statement of the conditions existing at the time of observation. Moreover profound change may be caused not only by mechanical forces but also by mental influences.' Barclay has shown that emotional disturbance, such as fear, may produce relaxation in the tone of the gastric musculature and a consequent drop in the position of the stomach. Thus the sudden banging of a door during a screen examination caused the lower border of the stomach to drop from the level of the umbilicus almost into the pelvis.

Influence of emotions on position of stomach

Mobility of colon and caecum

Radiological investigations have shown the position of the colon to be as variable as that of the stomach. The caecum may lie in any position between the upper border of the iliac crest and the pelvis, and the transverse colon varies to a remarkable extent in the level at which it crosses the abdomen. Although many symptoms, including chronic constipation, have been ascribed to coloptosis, there is no radiological or clinical evidence to support such a view.

Motility of stomach

The motility of the stomach in no way depends on its position in the abdomen. It can be shown that a stomach, the greater curvature of which is within the true pelvis, can empty in normal time provided there is no obstruction at the pylorus.

Although there is no evidence that the abdominal viscera occupy fixed 'normal' positions in the abdominal cavity, nevertheless it must be admitted that the viscera in some individuals lie at lower levels than in others.

Many views have been put forward to explain how the abdominal viscera are retained in position. They are attached to the posterior abdominal wall by peritoneal ligaments, but these are relatively thin and lax and cannot hold the viscera in place. Indeed their laxity allows the free movements of such organs as the stomach and colon which take place with alterations in posture and respiration. One factor which helps to determine the shape and position of organs such as the stomach and colon is the general conformation or habitus of the individual. Thus the long-chested type with a narrow costal angle tends to have a narrow and elongated abdominal cavity which results in the stomach being elongated and vertical. On the other hand in the broad-chested individual with a wide costal angle the stomach tends to lie more horizontally and at a higher level in the abdomen. There has been much controversy as to the part played by the abdominal wall in the maintenance of the position of the viscera, and it has often been assumed that they are maintained in position by the intra-abdominal pressure due to the tonus of the abdominal musculature. Although the supports of the abdominal wall and of the pelvic floor are undoubtedly factors, atony of the abdominal muscles does not necessarily lead to ptosis of the abdominal viscera.

*Factors
determining
position of
viscera*

*Peritoneal
ligaments*

Habitus

*Abdominal
wall*

The position of the intra-abdominal viscera varies within very wide limits, not only in individuals but in the same person at different times and under different conditions. Moreover, it is clear that when viscera, such as the stomach or colon, are situated abnormally low, this is not inconsistent with perfect health and physical fitness.

Although the terms gastropptosis, coloptosis, nephropptosis, and hepatopptosis are often used to designate what is regarded as an abnormal position of the stomach, colon, kidney, and liver, it is unusual for a single organ to be situated abnormally low. Thus if the greater curvature of the stomach is situated in the pelvis the transverse colon will also be found at an even lower level.

3.—CLINICAL PICTURE

From what has been said above it is clear that the symptoms often ascribed to visceropptosis are certainly not due solely to an abnormally low position of the intra-abdominal viscera. Nevertheless certain symptoms are common in patients in whom the stomach, colon, and other organs appear to be abnormally pttosed. It is justifiable therefore to describe the symptoms so often attributed to visceropptosis. These are abdominal discomfort, flatulence, constipation, general weakness, and lassitude. The patients are almost always introspective and

*Symptoms
ascribed to
visceropptosis*

hypochondriacal and the vast majority are females, more commonly unmarried or childless married women.

Onset The history of the patient often shows that weakness and lassitude antedate the other symptoms, sometimes by many years. Even from childhood many of the patients have been regarded as weakly and of poor physique with deficient physical and mental energy.

Abdominal symptoms Abdominal symptoms attributed to visceroptosis are very variable; often they are not severe and are described by the patient as dragging sensations in the epigastrium or in either iliac fossa, commonly associated with backache. Sometimes burning or gnawing sensations may be complained of. At times there may be attacks of acute pain, particularly in one or other iliac fossa, which may suggest appendicitis or diverticulitis. During such an attack the caecum or pelvic colon is sometimes found to be tender, hard, and contracted, suggesting the condition often described as colospasm. Not uncommonly such attacks are followed by the passage of mucus and a diagnosis is made of muco-membranous colitis. (See also COLITIS, Vol. III, p. 294, and MUCOUS COLIC, Vol. VIII, p. 660.)

Flatulence Flatulence and distension are also common complaints. Considerable amounts of air may be eructated and the patient may be much worried by borborygmi and flatus. The patient, as a rule, regards these symptoms as caused by abnormal fermentation in the stomach or bowel, though in fact they are due to aerophagy. Constipation is perhaps one of the most constant accompaniments of supposed visceroptosis. Purgatives are usually taken daily, and, like those who suffer from mucous colic, these patients make a minute study of their faeces; often dissatisfaction with either their quality or quantity leads to great anxiety and distress. This may even induce them to have recourse to even more powerful purges which irritate the colon and may precipitate attacks of colospasm and the passage of mucus.

Appetite and diet Although the appetite is often fairly good, the patient often excludes first one article of diet and then another on the assumption that they increase the abdominal discomfort or produce pain; thus a very small amount of food is eaten, and as a result malnutrition and loss of weight aggravate the lassitude and fatigue which are often already prominent symptoms.

Vasomotor system The vasomotor system is often unstable. Attacks of palpitation and tachycardia are common together with dizziness or vertigo. These are sometimes associated with flatulence and distension, which produce alarming feelings of suffocation and dyspnoea.

Menstruation As might be expected in subjects of chronic inanition, there is often a disturbance of the menstrual functions, such as irregular menses, amenorrhoea, or dysmenorrhoea. There is an increased liability to infections, such as colds, influenza, sinusitis, and *Bact. coli* infections of the urinary tract. There is always some evidence of mental instability.

Mental changes Symptoms are described in excessive detail and their agonizing or intolerable character is much emphasized. Insomnia and nightmares are

common. The patient's lack of adaptation to her surroundings often renders family life difficult.

On physical examination there is little objective evidence of disease apart from evidence of malnutrition. The blood-pressure is usually below the average. There is often some degree of anaemia, probably due to the malnutrition. Radiological examination may show the stomach and colon to be low in position, but by no means constantly, and many patients who have been diagnosed as visceroptosis on the strength of general and local symptoms are found to have their viscera not unduly low. Not uncommonly the right kidney is easily palpable, and in some cases if the patient takes a deep breath the whole kidney descends below the ribs. As a rule it is not tender and no symptoms are attributed to it, unless they have been suggested by the ill-judged remarks of the practitioner. Examination of the gastric secretion with a fractional test-meal shows no constant findings and the amount of acid may range from hyperchlorhydria to achlorhydria.

Blood-pressure
Anaemia
Radiological findings

Test-meal

The clinical syndrome so often attributed to visceroptosis is really one of chronic invalidism, with a tendency for the patient to emphasize particularly symptoms referred to the alimentary tract. It is difficult to avoid the conclusion that at any rate the majority of patients with a diagnosis of visceroptosis belong to the class of patient who in the past was diagnosed as movable kidney, chronic intestinal stasis, or mucomembranous colitis, and who to-day is often classified under the heading of colospasm, enterospasm, or nervous dyspepsia. During recent years diagnoses of visceroptosis have become relatively uncommon and they will probably become even more so. Table I shows the cases, grouped in five-year periods, indexed since 1900 in the Guy's Hospital clinical reports under the headings visceroptosis (including enteroptosis), movable kidney, chronic intestinal stasis, gastropptosis, and coloptosis.

TABLE I.—Numbers of Cases of Selected Diagnoses indexed in Guy's Hospital Clinical Reports, 1900–33

YEARS	VISCEROPTOSIS	MOVABLE KIDNEY	CHRONIC INTESTINAL STASIS	GASTROPTOSIS	COLOPTOSIS
1900–1904	14	184	0	0	0
1905–1909	37	150	21	0	0
1910–1914	63	76	288	0	0
1915–1919	47	32	138	0	0
1920–1924	135	26	1	78	41
1925–1929	77	11	0	14	11
1930–1933	28	2	0	8	1

It is difficult to avoid the conclusion that fashions in diagnosis change. Thus in the course of thirty years movable kidney has practically disappeared and concurrently with its disappearance there was a

corresponding rise in the number of patients diagnosed as visceroptosis and chronic intestinal stasis.

A progressive decrease in the number of patients with diagnoses of visceroptosis, enteroptosis, and gastropotosis is shown in Table II.

TABLE II.—Numbers of Diagnoses of Visceroptosis, Enteroptosis, and Gastropotosis made at the London Hospital from 1920 to 1934, arranged in Quinquennial Periods

YEARS	MALES	FEMALES	TOTAL
1920 to 1924 -	164	533	697
1925 to 1929 -	135	484	619
1930 to 1934 -	40	246	286

For the last two years for which figures are available at the London Hospital (1935 and 1936) the total number of cases with these diagnoses had fallen to 30 and 45 respectively.

Although visceroptosis is not the common condition it was at one time thought to be, there are some uncommon clinical conditions in which ptosis of certain abdominal organs appears to be a causal factor. These are nephroptosis with the production of attacks simulating renal colic known as Dietl's crises (see Vol. VII, p. 389), obstruction of the third part of the duodenum as a result of compression by the root of the mesentery (duodenal ileus, see Vol. VII, p. 248), and gastropotosis with the production of gastric stasis.

*Nephroptosis,
duodenal
ileus, and
gastropotosis*

Gastropotosis

Gastropotosis may perhaps in certain circumstances produce demonstrable delay in the passage of food from the stomach. A stomach the greater portion of which is situated in the pelvis shows normal tone and peristalsis and evacuates its contents without undue delay, because in the great majority of instances of gastropotosis the pylorus and duodenum are also lying at a low level in the abdomen. If, however, the retro-peritoneal portion of the duodenum, i.e. its second or descending portion, remains firmly anchored to the posterior wall of the abdomen, this may produce a kinking at the junction of the first and second parts of the duodenum which may interfere with the normal evacuation of the stomach. Thus when the stomach is shown by X-ray examination to be situated unduly low it is important to localize the level of the second portion of the duodenum when the patient is examined erect. If the duodenum has not dropped with the stomach it can usually be shown that though the duodenal cap (the first part of the duodenum) fills readily the opaque meal does not pass with normal rapidity into the second and third parts of the duodenum. If, however, the patient lies down, particularly if she lies on her right side, the pylorus and stomach assume a more elevated position, the kink is obliterated, and the opaque meal passes with normal speed through all portions of the duodenum. The partial obstruction is manifested by abdominal discomfort, which starts as a meal is being taken and is at its worst when the stomach is full. If the patient lies down on the right

*Cause of
interference
with
evacuation*

side the symptoms rapidly abate. A large and bulky meal is more likely to produce symptoms than a small meal. Gastric stasis of this type is but rarely produced by gastropotosis, and in the great majority of instances the stomach empties normally.

Ptosid of the liver may be associated with a general visceroptosis. In cases of megacolon, or Hirschsprung's disease (see Vol. VIII, p. 470), the liver may be rotated to the right so that the right lobe extends well below the umbilicus and almost into the right iliac fossa. Usually no special symptoms are produced by hepatoptosis but it is important to avoid regarding the condition as due to enlargement or growth. By percussion it is often possible to demonstrate that the upper border of the liver is abnormally low. *Ptosid of liver*

Ptosid of the spleen is extremely rare except when the spleen is enlarged as in chronic myeloid leukaemia, in which disease the spleen is often dropped and rotated and may even be found in the pelvis. Symptoms are usually absent unless torsion of the pedicle occurs. *Ptosid of spleen*

4.—COURSE AND PROGNOSIS

The symptom-complex so commonly described as due to visceroptosis is so often associated with a psychological and physical inferiority, which is to some extent inherent and environmental, that when symptoms have once become firmly established the outlook as regards cure is necessarily poor. Without a complete change in personality and constitution it can hardly be expected that the mental outlook and habits can be altered. Moreover, some of these patients 'enjoy ill-health' and would be the last to desire to exchange their chronic invalidism for a robust normal life. In chronic cases therefore, when the symptoms have been present for years, there is little hope of effecting more than a temporary improvement, particularly if unnecessary and ill advised surgical operations, such as nephropexy, colopexy, gastroplasty, or even appendectomy, have been performed. When the symptoms have been of relatively short duration and the patient is co-operative the outlook is better, at least as regards relief and improvement if not as regards complete cure. Though the condition may make life a burden, if not to the patient at any rate to her relatives, it does not in itself shorten life except in so far as the inanition and general physical unfitness may render her an easier prey to intercurrent illness. *Psychological element*

5.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A careful X-ray examination of the stomach and duodenum should detect the rather unusual cases of gastropotosis in which fixity of the duodenum has caused delay in the emptying of the stomach.

The symptoms attributed to visceroptosis are so vague and variable that a carefully taken history in conjunction with a consideration of the patient's attitude and personality are often almost sufficient to exclude

diseases which produce well defined symptom-complexes, such as duodenal ulcer, gastric ulcer, or renal and biliary colic. The duration of symptoms is often sufficient to exclude malignant growths. These patients may sooner or later develop some organic disease and, as it is most important for the practitioner to satisfy himself that gross organic disease is absent, it is usually wise to have the patient thoroughly investigated with X-rays of the alimentary tract and the gall-bladder, a fractional test-meal, and examination of several faecal specimens for occult blood. For the latter the patient must be kept on a diet free from meat, fish, green vegetables, and fruit for at least four days. Often in addition an X-ray examination of the lungs is desirable to exclude a latent tuberculosis and, if there is any suggestion of anaemia, a blood count. Hypochromic anaemia, so often found in women with hypochlorhydria, is a common cause of chronic ill-health. The chronic gastritis which is so common in this type of patient may suggest a diagnosis of visceroptosis.

From latent tuberculosis

From hypochromic anaemia

The diagnosis of nephroptosis with Dietl's crises is described in Vol. VII, p. 389, and that of duodenal ileus in Vol. VII, p. 250.

It is doubtful if it is ever wise to tell a patient that he or she is suffering from visceroptosis. To the lay mind the statement that the stomach, bowels, or kidneys are dropped or misplaced offers a reasonable explanation for symptoms of any and every kind, which is only too readily accepted by the patient. Moreover, the idea is a great deal easier to implant than to eradicate from the patient's mind. Diagnoses such as nerve exhaustion, nervous dyspepsia, or colospasm are likely to have less deleterious effects.

6.—TREATMENT

Preventive

Rest after parturition

It has often been stated that visceroptosis is likely to follow a confinement if the patient is not kept sufficiently long in bed. The abdominal muscles stretched during pregnancy are left lax after parturition and if the patient gets up and about too early the lax abdominal wall and pelvic floor allow the viscera to descend. Though without doubt an adequate period of rest, certainly not less than twelve days, should be insisted on after a confinement, it is very doubtful if this is an important factor in the production of visceroptosis. Quite apart from other arguments most patients in whom the diagnosis is made have not borne children.

Environmental factors

Very often the symptom-complex designated as visceroptosis is initiated in early life or even in childhood. The patient may have been an only child brought up in an atmosphere of invalidism and maternal anxiety. Labouring under the defects of an inferior constitution a sense of inferiority develops, which may later lead to chronic invalidism as a refuge, particularly if the environment, whether occupational or domestic, is unsatisfactory. A general improvement in the management of children, both before and during school life, will without doubt tend to diminish the incidence of chronic invalidism in later life.

Specific

As most of these patients suffer from undue fatigue, rest must be insisted on, in varying degree according to the severity of the individual case from rest in bed to curtailment of unnecessary activities. The patient is constitutionally under average, both physically and mentally, and the degree of activity allowed must be adjusted to her powers. She should go to bed early and if there is difficulty in getting to sleep a dose of bromide at night is often both effective and harmless. Only too often the patient has a dread of sleeping draughts and it may be wise to say that she is being given a tonic rather than a sedative. In severe cases, when the patient is being kept at rest in bed, a course of general massage is often of value.

*Rest**Sedative**Massage*

The posture of these patients is often defective and much can be done to correct this by graduated exercises and gymnastics, but they should not be severe enough to produce fatigue and exhaustion. The exercises should be performed under the supervision of an expert in remedial exercises; moreover, it is always more satisfactory if they can be done in a class rather than individually, as the presence of other patients tends to produce a competitive spirit and an atmosphere of cure. The exercises consist mainly of active movements of the abdominal muscles and diaphragm, which in most of these patients is unduly low with a restricted respiratory excursion.

Correction of faulty posture

In the past abdominal belts, either elastic and webbing or leather and metal, were almost invariably ordered for patients who were supposed to be suffering from visceroptosis. It was assumed that a belt restored the dropped viscera to a normal position. Although X-ray examination demonstrates clearly that a belt has not any effect whatever on the position of the viscera, a proportion of patients obtain subjective benefit from a belt. Whether this is due only to moral support or whether the belt may increase the intra-abdominal pressure and perhaps secondarily benefit the vasomotor system is uncertain. At any rate a belt is well worth a trial, the most comfortable type being the elastic and webbing.

Abdominal belts

Patients often subsist on an inadequate diet, not so much because appetite is lacking as because they have cut out of their diet successively various kinds of food on the assumption, usually wrong, that these disagree with them. As a result of a continued low diet feelings of fatigue and exhaustion are aggravated and sometimes there may be almost emaciation. It is wise to forbid, at any rate for a time, all articles of diet which leave a large cellulose residue, as many of these patients are liable to attacks of colospasm and muco-membranous colitis. All vegetables should be excluded unless sieved, particularly salads, cucumber, and tomatoes. Fruit-juice is desirable but all pips and skins must be avoided. Highly spiced food, such as game, sauces, and shell-fish, are undesirable. If distension and flatulence are troublesome, potatoes and rice should not be eaten, particularly if the flatulence

Diet

appears to be mainly colonic. The patient should eat slowly and chew the food well, and meals should be at regular times and not hurried.

*Treatment of
gastroptosis*

In the rare cases of gastroptosis in which fixity of the duodenum produces kinking with slow evacuation of the gastric contents relief is often obtained if the patient lies on the right side for half an hour to an hour after meals. The latter should be small and rather frequent. If symptoms are severe a period of complete rest in bed with the foot of the bed elevated may be necessary.

Drugs

Most of these patients suffer from constipation and many of them take powerful purgatives daily, thereby irritating a colon which is usually already over-irritable. The constipation is due not to obstruction or kinking associated with ptosis but to the general poor physical condition of the patient and the unsatisfactory abdominal musculature, which renders the act of defaecation ineffective. All purgatives should be stopped and liquid paraffin given in divided doses after meals in order to avoid the formation of scybala. In some cases enemas may be necessary. In patients who have attacks of colospasm or muco-membranous colitis an antispasmodic mixture is often of value, such as tincture of belladonna 5 minims, tincture of hyoscyamus 20 minims, and peppermint water to $\frac{1}{2}$ fluid ounce. This may be taken thrice daily before meals.

*Anti-
spasmodics*

*Attitude of
practitioner*

In these difficult and distressing cases it is most important for the practitioner to be sympathetic and tactful. When the patient has been thoroughly investigated and all findings are negative her practitioner must be particularly careful not to convey the impression that he thinks there is nothing wrong or that the patient's ills are purely imaginary. Such an attitude at once makes the patient lose confidence and further co-operation between patient and practitioner is impossible. It should be explained to the patient that the digestive mechanism, though perfect in itself, depends for its satisfactory functioning on nervous control. Examples may be given of the effects of exhaustion, anxiety, or fear on the appetite and digestion. The mechanism of aerophagy should be explained to patients who are troubled with eructations and borborygmi (see AEROPHAGY, Vol. I, p. 256). As a rule these symptoms are attributed to 'fermentation' and if the real nature of the condition is explained symptoms are often much relieved. An unfavourable environment may often play an important part but unfortunately this is often an unavoidable factor. A sympathetic and confidential talk may, however, be of the greatest value in helping the patient to adapt herself.

Surgical

The only two conditions associated with ptosis in which any surgical interference is justifiable are Dietl's crises (see Vol. VII, p. 390) and duodenal ileus (see Vol. VII, p. 250).

Since about the beginning of this century innumerable operations have been devised for the supposed replacement of dropped organs, and the results are almost always disastrous. Sometimes as a result of the rest

enforced by the operation and perhaps the personality of the operator there may be a short temporary improvement but usually within six months the patient is as bad or worse than before operation. In such cases the recurrence of symptoms is often attributed to 'adhesions' and the patient is lucky if she is not subjected to secondary operations. Fortunately surgeons have become more hesitant than formerly about operating on chronic abdominal invalids. At Guy's Hospital in the five years 1927 to 1931 there were only five nephropexies and only two colopexies performed. This is a striking contrast to the figures for 1920 to 1924, when there were 15 nephropexies and 30 colopexies, and for the years between 1911 and 1915 when there were no less than 286 colectomy and short circuit operations, most of which were performed on patients of the type often grouped as visceroptosis. Unfortunately since about 1920 there has been a big increase in the number of operations for chronic appendicitis, many of which have been performed for the cure of vague dyspeptic symptoms.

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VISION, SYMPTOMATIC DISTURBANCES

See ASCARIASIS, Vol. II, p. 151; DIETETIC DEFICIENCY DISEASES, Vol. IV, p. 57; EPILEPSY, Vol. V, p. 103; JAUNDICE, Vol. VII, p. 266; MIGRAINE, Vol. VIII, p. 607; PSYCHONEUROSES AND PSYCHOTHERAPY, Vol. X, p. 246; VITAMINS, p. 594; and other strictly eye conditions appearing under their own titles

VITAMINS

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Reference may also be made to the following titles:

BERI-BERI	INFANT FEEDING
DIETETIC DEFICIENCY	PELLAGRA
DISEASES	RICKETS
FOOD	SCURVY

1.-DEFINITION

1601.] Vitamins may be defined as substances distributed in foods in quantitatively small amounts, distinct from the main components (carbohydrate, fat, protein, mineral salts, and water) which are needed for the normal nutrition of the organism, and absence of which is the cause of specific 'deficiency diseases'. The more important of these vitamins, from the standpoint of clinical medicine, are no doubt the following. (a) Water-soluble group: (i) vitamin B₁, which protects against beri-beri and nutritional polyneuritis; (ii) the 'P-P' or pellagra-preventing factor, a part of the so-called 'vitamin B₂ complex'; and (iii) vitamin C which protects against scurvy. (b) Fat-soluble group: (iv) vitamin D which protects against rickets, as well as osteomalacia and nutritional tetany, and (v) vitamin A, the 'anti-xerotic' factor. Vitamin E (anti-sterility factor) is probably of significance for human beings, and vitamins 'P', 'H', and others (see p. 598) possibly so. For chemical names or other synonyms see p. 575.

2.-HISTORICAL

Recognition of the existence of vitamins has grown gradually. The first step in a long series of developments leading eventually to the

'vitamin hypothesis' may be discerned in some early observations on deficiency diseases, especially on scurvy and beri-beri.

*Empirical
cures of
scurvy,
beri-beri,
and rickets*

Early in the seventeenth century (1601) Sir James Lancaster introduced the regular use of oranges and lemons into the ships of the East India Company as a preventive against scurvy. Many others, during the seventeenth and eighteenth centuries, repeatedly confirmed the fact that fresh fruits and vegetables were effective in curing or preventing the disease. In 1885 Takaki was able to stamp out beri-beri in the Japanese navy by changes in the diet. The nature of the dietetic error responsible for these two diseases, however, was not yet understood, although it may be recalled that a far-sighted physician had predicted in 1840 that scurvy is 'due to the lack of an essential element which it is hardly too sanguine to state will be discovered by organic chemistry or the experiments of physiologists in a not too distant future' (Budd). Towards the end of the nineteenth century the view began to be expressed by paediatricians that 'rickets is produced as certainly by a rachitic diet as scurvy by a scorbutic diet'.

*Discovery of
experimental
avitaminoses*

In 1890 Eijkman, in the Dutch East Indies, made the important discovery of experimental beri-beri in fowls. From 1890 to 1897 he carried out the earliest work on the extraction of the antineuritic substance (now called vitamin B₁), which he found to be present in the bran of rice but not in polished rice. But the first to appreciate clearly that beri-beri was due solely and simply to a dietary deficiency and was not caused by any positive agent or toxin, was Eijkman's collaborator, Grijns (1901). In 1907 Holst and Frölich in Christiania discovered experimental scurvy in guinea-pigs. With Eijkman's pioneer work on beri-beri in mind they considered this likewise to be a deficiency disease and set out to examine the properties of the anti-scorbutic substance (now vitamin C).

*The concept
of vitamins*

By 1906 Hopkins could refer to scurvy and rickets as 'diseases in which for long years we have had knowledge of a dietetic factor'. He realized, moreover, that the errors in the diet 'although still obscure' were 'certainly of the kind which comprises the minimal qualitative factors'. In 1912 Funk, then working on the anti-beri-beri factor, propounded his 'vitamine' theory—i.e. he postulated the existence of separate anti-beri-beri, antiscurvy, antirickets, and antipellagra 'vitamines'.

*Experiments
on 'synthetic
diets'*

In the meantime experiments had been in progress attacking the problem from an entirely different angle—investigating not deficiency diseases as such but determining what constituted a physiologically complete diet. Lunin, a pupil of the Swiss biochemist Bunge, first showed in 1881 that animals failed to thrive when kept on an artificial regimen comprising the then known constituents of food, i.e. re-purified fat, protein, carbohydrate, mineral salts, and water. He concluded that 'a natural food such as milk must therefore contain besides these known principal ingredients small quantities of other and unknown substances essential to life'. Similar conclusions were reached by various other

workers, of whom the most notable were Socin (1891) and Stepp (1909); mention must also be made of Coppola (1890), Hall (1896), Häusermann (1897), Henriques and Hansen (1905), Falta and Noeggerath (1906), and Jacob (1906). The eminent Dutch physiologist Pekelharing published in 1905 the statement—generally overlooked at the time—that the unknown substances must be effective in very minute amounts, for he had found that quite small supplements of natural foods added to the artificial synthetic ration were sufficient to afford protection. An independent and more detailed study by Hopkins (1912) had as its principal conclusions: (i) that an insignificantly small addition of milk would suffice to render the purified diet adequate; and (ii) that the animals ceased to grow while still eating sufficient *in quantity* to support good growth.

The year 1912 may be said to mark the beginning of modern intensive work on vitamins. Hopkins' celebrated paper and Funk's review, published a few months earlier, for the first time attracted world-wide attention to 'the vitamin question'. For a few years longer nevertheless the existence of vitamins was still disputed.

In 1929 the importance of the pioneer experiments of Eijkman and of Hopkins was recognized by the award to them jointly of the Nobel Prize for Medicine.

3.—CLASSIFICATION AND ENUMERATION

(1)—Separation of 'Fat-Soluble' and 'Water-Soluble' Factors

The first real indication of the multiplicity of vitamins came in 1915 when McCollum and Davis in America showed that, with the rat as an experimental animal, at least two accessory factors were needed for growth. One was present in fatty and the other in non-fatty foods. These were named respectively 'fat-soluble A' and 'water-soluble B'.

(2)—Growth of the Vitamin Alphabet

Before long it became recognized that what was called 'water-soluble B' had the properties of the antineuritic (anti-beri-beri) 'vitamine'. To avoid confusion the two systems of nomenclature were combined. At the suggestion of J. C. Drummond 'water-soluble B' was re-named vitamin B, the terminal *e* of the word *vitamine* being omitted to avoid any unwarranted implication that it was of the chemical nature of an amine. Similarly 'fat-soluble A' was renamed 'vitamin A'. The most noticeable effects of its deficiency were found to include loss of growth, xerophthalmia, and increased liability to infection, especially of the respiratory system. It soon became apparent that the antiscurvy factor had quite different chemical properties from either 'vitamin B' or 'vitamin A'. It was accordingly given the next letter in the alphabet and became vitamin C. A little later it was proved conclusively that

'Fat-soluble A' and 'water-soluble B'

Vitamin B

Vitamin A

Vitamin C

Vitamin D

<i>Vitamin E</i>	experimental rickets in dogs was due to the absence of a fat-soluble vitamin (Mellanby, 1918). At first it was thought to be identical with vitamin A; but, later, differences in distribution and chemical properties were established (McCollum, Simmonds, Becker, and Shipley, 1922) and it was accordingly named vitamin D. A new factor, vitamin E, needed to ensure normal reproduction in the rat, was discovered by Evans and Bishop in California in 1923. Confirmatory evidence was obtained independently and almost simultaneously by Sure and by Mattill, also in America.
<i>Vitamin B₁ and 'vitamin B₂'</i>	In 1926 Goldberger proved, as Funk had predicted, that pellagra was caused by deficiency of a vitamin. He showed that it had a distribution similar to that of the anti-beri-beri factor but was more stable to heat. Accordingly 'vitamin B' was then split up into vitamin B ₁ , the anti-beri-beri factor proper, plus the new B ₂ , or more heat-stable component.
<i>Vitamin B₂ as a complex</i>	Vitamin B ₂ , thus defined as 'the more heat-stable part of the "vitamin B ₂ complex"', has proved in turn to be itself complex. The first component to be characterized was riboflavin (Kuhn, György, and Wagner-Jauregg, 1933), and the second 'vitamin B ₆ ' (György, 1934). In 1935 Birch, György, and Harris showed that the pellagra-preventing factor proper was a third component, distinct from both lactoflavin or vitamin B ₆ . This 'P-P' vitamin has recently been identified with nicotinic acid. It is not yet known if deficiencies of vitamin B ₆ and lactoflavin occur in man.
<i>American nomenclature</i>	In the United States of America the terms 'vitamin B' and 'vitamin G' are sometimes used in the sense in which vitamin B ₁ and vitamin B ₂ are used elsewhere.

(3)—List of the Better-Known Vitamins

<i>Constitution and synthesis</i>	During the last decade (1928–38) the chemical constitutions of the better-known vitamins (including A, B ₁ , C, D, and E) have been established; they have been isolated in a state of purity; and several of them (including A, B ₁ , C, and E) have been synthesized in the laboratory. Vitamin A (C ₂₀ H ₂₉ OH) is chemically related to the naturally occurring hydrocarbon β -carotene (C ₄₀ H ₅₆) which shares its biological activity. Vitamin B ₁ (C ₁₂ H ₁₆ N ₄ OS) has been given the name of aneurin (or thiamin in U.S.A.). Vitamin C, ascorbic acid (or cevitamic acid in U.S.A.) is C ₆ H ₈ O ₆ . There are several forms of vitamin D, the most important being calciferol or 'vitamin D ₂ ' (C ₂₈ H ₄₃ OH) and 'vitamin D ₃ ' (C ₂₇ H ₄₂ OH). Vitamin E, α -tocopherol, has the formula C ₂₉ H ₅₀ O ₂ ; there is also a β -tocopherol which has similar biological activity (for rats).
<i>Chemical names and empirical formulae</i>	
<i>Summaries</i>	Further information about these factors, and about lactoflavin and vitamin B ₆ (the human relations of which are less clear), is given in Tables I and II.

TABLE I.—List of Better-Known Vitamins

NAME	WHETHER FAT-SOLUBLE OR WATER- SOLUBLE	CORRE- SPONDING DEFICIENCY DISEASE	EMPIRICAL FORMULA	CHEMICAL NAME	SIZE OF 1 INTERNATIONAL UNIT	DAILY PROTECTIVE DOSE		APPROXIMATE DAILY REQUIREMENT OF HUMAN BEING	
						FOR RATS	FOR GUINEA- PIGS	ADULT *	INFANT
Vitamin A	Fat-soluble	xerosis	$\begin{Bmatrix} C_{20}H_{30}OH \\ C_{40}H_{66} \end{Bmatrix}$	vitamin A β -carotene	.. 0.0006 mgm.	5 I.U.	.. ?	3,000 I.U. }(=2 mgm.)	..
D	"	rickets	$\begin{Bmatrix} C_{28}H_{43}OH \\ C_{27}H_{42}OH \end{Bmatrix}$	calciferol 'D ₂ '	0.000,025 mgm.	1 I.U.	?	}	500 I.U.
E	"	sterility	$\begin{Bmatrix} C_{29}H_{50}O_2 \\ C_{28}H_{48}O_2 \end{Bmatrix}$	α -tocopherol β -tocopherol	0.1 mgm. ..	? ..	?	..
$\begin{Bmatrix} B_1 \\ B \\ \begin{Bmatrix} B_2 \\ B_6 \end{Bmatrix} \\ \begin{Bmatrix} P-P \\ B_2 \\ B_6 \end{Bmatrix} \\ \begin{Bmatrix} Ribo- \\ flavin \end{Bmatrix} \end{Bmatrix}$	Water-soluble	beri-beri	$C_{12}H_{10}N_4OS$	aneurin (thiamin)	0.003 mgm.	2 I.U.	?	300 I.U. (=1 mgm.)	..
	"	pellagra	$C_6H_5NO_2$	nicotinic acid	?	? 100 mgm.	..
	"	'rat pellagra'	$C_8H_{12}O_3NCl$	adermin	..	0.01 mgm.	?	?	..
	"	..	$C_{17}H_{20}N_4O_6$	riboflavin	..	0.01 mgm.	?	?	..
	"	scurvy	$C_6H_8O_6$	ascorbic acid	0.05 mgm.	0	1.5 mgm.	25 mgm.	..

* Relatively more needed during lactation and pregnancy.

TABLE II.—Sources of Better-Known Vitamins

NAME			PRINCIPAL SOURCES (WITH APPROXIMATE ACTIVITY,* I.U. OR MGM. PER 100 GRAMS)	
Vitamin A	—	—	Halibut-liver oil	3,000,000–15,000,000 I.U.
			Cod-liver oil	50,000–200,000
			Liver, calf	50,000–150,000
			Butter	2,000–3,000
			Red-palm oil	50,000–200,000
			Spinach	3,000–10,000
			Carrot	2,000–6,000
D	—	—	Tuna-liver oil	2,000,000–6,000,000 I.U.
			Halibut-liver oil	100,000–300,000
			Cod-liver oil	10,000–30,000
			Herring-body oil	10,000–20,000
			Cacao-shell oil	30,000
			Egg yolk	200–400
			Butter	10–100
E	—	—	Wheat-germ oil	.
			Rice-germ oil	..
			Cotton-seed oil	..
			Green leaves	..
B ₁	—	—	Dried brewers' yeast	1,000–2,000 I.U.
			Barley germ	1,500
			Wheat germ	500–1,000
			Rice bran	500
			Oatmeal	300
			Wheat, whole grain	100–200
			Wholemeal bread	100
			Peas	100
			Haricot beans	100
P-P	—	—	Egg yolk	100
			Yeast	.
			Liver	..
			Wheat germ	..
			Salmon	..
B ₆	—	—	Egg yolk	..
			Fish muscle	..
			Cereals	..
Riboflavin	—	—	Molasses	..
			Yeast	..
			Kidney	..
			Liver	..
Vitamin C	—	—	Egg white	..
			Milk	..
			Black currants	200 mgm.
			Paprika	200
			Orange-juice	50–70
			Lemon-juice	40–60
			Cabbage	30–60
			Spinach	30–60
			Tomato-juice	20–30

* Activities vary considerably from specimen to specimen, and these figures should be taken merely as representative of an average range of values. Individual samples may be considerably higher or lower—see Fixsen and Roscoe (1938).

4.—WATER-SOLUBLE VITAMINS

(1)—Vitamin B₁ and Beri-Beri(a) *Vitamin-B₁ Deficiency*

1602.] In man, as in experimental animals, beri-beri (see Vol. II, p. 314) results from the consumption of a diet deficient in vitamin B₁—e.g. a regimen of polished rice, or the too exclusive use of white bread. The principal features include loss of appetite, marasmus, cardiac abnormalities, paresis or paralysis, and sometimes oedema; the characteristic lesion is a demyelination of peripheral nerves, the so-called polyneuritis.

*Identity of
experimental
and clinical
beri-beri*

Any lingering doubt about the identity of clinical beri-beri with avitaminosis B₁ must now be set at rest since it has recently been repeatedly demonstrated that a spectacular cure follows treatment with massive doses of the pure crystalline vitamin (see, for example, Hermano and Eubanas, 1935; Platt and Lu, 1936; Hawes *et al.*, 1937; Hashimoto, 1937; Yudkin, 1938). In severe cases, or in 'fulminating' beri-beri with cardiac failure, doses of as much as 3,000 units are given, by injection.

*Cure with
pure vitamin
B₁*

Beri-beri is still very prevalent in the East Indian Archipelago and in parts of Japan, China, and South India. For example, in Japan 10,000 to 20,000 deaths yearly were recorded during the period 1928–32.

Prevalence

The daily requirement for vitamin B₁ for an adult is probably somewhere between 300 I.U.—described as the 'physiological minimum', and 600 I.U.—the 'desirable intake' (Baker, Wright, and Drummond, 1937). Relatively more is needed by pregnant and lactating females, and also by infants and growing children and those doing severe physical exercise.

*B₁ require-
ment*

In North America a series of carefully controlled dietary experiments suggests that a partial deficiency of the vitamin (hypovitaminosis) may be not uncommon even under Western conditions. The symptoms are somewhat vague but include diminished appetite, subnormal gains in weight, and sometimes hypotonicity of the gastro-intestinal tract and constipation. The indication of a deficiency is generally furnished by the improved rate of growth seen when extra vitamin B₁ is given, e.g. in the form of wheat germ or preparations of wholemeal cereals.

*Hypovitamin-
osis B₁*

An important advance in the past few years has been the recognition that polyneuritis, or other symptoms of avitaminosis B₁, may not uncommonly be caused by a 'conditioned deficiency' due, that is, to a faulty absorption of the vitamin (as with a gastro-intestinal obstruction) or to loss of appetite. Alcoholic polyneuritis and polyneuritis in pregnancy are examples. Opinion at present is rather divided on the question whether certain other types of neuritis may respond to large doses of vitamin B₁ (see Vorhaus, Williams, and Waterman, 1935), but there is growing evidence that a number of obscure cardiac disorders may be related to deficiency of the vitamin (Weiss and Wilkins, 1936; Abt, 1935).

*'Conditioned
deficiency'*

Diagnosis of partial deficiency

Tests on urine have been introduced to determine the level of nutrition of the human subject with regard to vitamin B₁, and hence to diagnose the presence or absence of a state of deficiency (Harris and Leong, 1937; Harris, Leong, and Ungley, 1938; Wang and Harris, 1939).

Prophylaxis and treatment

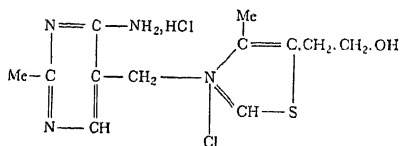
In beri-beri or in nutritional polyneuritis treatment is best effected by crystalline vitamin B₁ or at least a highly potent concentrate; a nourishing mixed diet is also provided to rectify any other concurrent errors. When it is desirable to increase the intake of vitamin B₁ as a general prophylactic measure, this can readily be done by the addition of wheat germ or by the substitution of wholemeal for white bread. In the East parboiled or unpolished rice should be substituted for polished rice; or peas, beans, or lentils may be provided. Tiki-tiki (extract of rice polishings) and dried yeast have also been used successfully. Certain yeast-extracts are relatively inactive.

*(b) Properties of Vitamin B₁**Chemical nature of vitamin B₁*

Thirty years of intensive effort by investigators all over the world preceded the eventual isolation of crystalline vitamin B₁ by Jansen and Donath in 1926. A distinctive feature from the chemical standpoint is the presence of sulphur in the molecule (Windaus *et al.*, 1932). A structural detail proved by synthesis and especially worthy of note is the peculiar thiazole ring system, linked with a substituted pyrimidine ring (Williams and Cline, 1936; Andersag and Westphal, 1937; Todd and Bergel, 1937).

Chemical properties

Vitamin B₁ is a base, forming salts, e.g. the chloride-hydrochloride shown in the structural formula below. The fact that it is fairly readily destroyed by heat explains why it is absent from certain canned products or sterilized foods. It is easily soluble in water and alcohol but not in fat solvents. It can be adsorbed on fullers' earth and certain other substances: the 'pulvis vitamini B₁' of the British Pharmacopoeia is such an adsorbed preparation, supplying 100 units per gram. Its use in clinical practice is now being largely superseded by the pure crystalline vitamin.

Chloride-hydrochloride of vitamin B₁*Distribution in foods*

Vitamin B₁ is widely distributed, but in moderate amounts only, in most natural foods. The best sources include wheat germ, wholemeal cereals, dried yeast, and pulses. White bread contains negligible amounts, but it is present in wholemeal bread or in 'germ bread'. The classical methods of assaying for vitamin B₁ were by the cure of polyneuritis in pigeons or by growth-tests on rats; more recently an electrical cardiological method has been introduced and chemical procedures are now being worked out.

Methods of assay

(c) *Physiological Action of Vitamin B₁*

It is now known that vitamin B₁ is concerned in the intermediate metabolism of carbohydrate. In animals or humans suffering from a deficiency of the vitamin, excessive amounts of lactic and pyruvic acids accumulate in the blood and tissues. Administration of vitamin B₁ rectifies this metabolic error by accelerating the removal of these substances. In fact it has recently been proved by Lohmann and Schuster (1937) that a pyrophosphate ester of vitamin B₁ functions as the co-enzyme needed by the enzyme carboxylase. (Carboxylase is an enzyme concerned in the break-down of pyruvic acid in the intermediate metabolism of carbohydrates.) Peters (1936) had previously shown that vitamin B₁ *in vitro* can restore the lost oxidative activity to avitaminous tissues respiring in the presence of pyruvic or lactic acids. *Relation to carbohydrate metabolism*

(2)—**Vitamin B₂ Complex and the Pellagra-Preventing (P-P) Factor**

1603.] At one time pellagra was commonly spoken of as being caused by a deficiency of vitamin B₂. As mentioned on page 574, it is now recognized that vitamin B₂ is a complex consisting of several different vitamins, of which the pellagra-preventing (P-P) factor, nicotinic acid, is but one constituent.

(a) *Pellagra in Man and Experimental Animals*

Pellagra in man is associated with subsistence on a one-sided diet—generally one that is composed principally of highly milled maize, e.g. in the 'three Ms' of the southern states of the U.S.A., maize, molasses, and meat (salt pork). The consumption of maize, however, is by no means a necessary condition for its production, as is shown by its incidence in certain institutions for the insane and in other places where maize is not included in the dietary. In this connexion too the fact that pellagra may occur as a 'conditioned deficiency' (see p. 577) in alcoholic addiction and other disorders should be borne in mind. The view that a toxin present in deteriorated maize causes the disease does not seem in conformity with the observation that experimental pellagra, whether in man, dogs, monkeys, or pigs, can be produced by diets not necessarily containing any maize and can be as abruptly and dramatically cured by administration of the appropriate vitamin—i.e. nicotinic acid. *Pellagra and maize*

The principal centres of endemicity of human pellagra are in the southern states of the U.S.A., Egypt, Italy, and the Balkan States. In the Mississippi basin and neighbouring districts 170,000 cases are reported to have occurred in 1917 and 120,000 in 1927; according to official returns the number of deaths in the United States was more than 10,000 in 1915, or 7,000 in each of the years 1928, 1929, and 1930. In Rumania 75,000 cases occurred in 1920, and in Italy 34,000 in 1910. The disease in Europe is much less severe than that in America and the mortality rate far lower. As the pellagra-producing diet has been *Prevalence*
Clinical characterist

described as 'the three Ms', so the most characteristic aspects of the clinical picture have been named 'the three Ds'—diarrhoea, dermatitis, and dementia. The dermatitis, with its symmetrical distribution on the hands, the forearm, and the face, is the most diagnostic feature. (For clinical picture see PELLAGRA, Vol. IX, p. 473.)

(b) *Dietary Origin of Pellagra*

Pellagra a deficiency disease

Proof that pellagra was not conveyed by infection but was a deficiency disease was first furnished by Goldberger and his co-workers (1914 and 1915), who in the first place pointed out that those who fell victims to the disease were existing on a poorer diet than those in the same community who escaped, e.g. the doctors and nurses in hospital. Secondly, he was able invariably to cure, prevent, or produce pellagra experimentally in human subjects by dietary changes. All attempts to convey the disease by inoculation with extracts of blood, nasopharyngeal discharges, faeces, urine, or desquamating epithelium failed.

(c) *The Pellagra-Preventing Factor*

Protein theory

For some years, about 1916–26, it was believed that an inferiority in the biological value of the protein consumed was the cause of pellagra. According to this view pellagra could be regarded as due to the deficiency of some essential amino-acid, perhaps tryptophane. Disproof came when Voegelin in 1920 cured pellagra with protein-free and amino-nitrogen-free extracts. These extracts, as Voegelin showed, were often rich in 'vitamin B', as measured by growth-tests on rats. Nevertheless, certain more highly purified concentrates of the anti-neuritic vitamin were not necessarily effective. In other words the anti-pellagra factor seemed to be something in the crude vitamin B other than the part now called B₁. Goldberger in 1926 gave conclusive proof of this distinction; he showed that the pellagra-preventing factor differed from the antineuritic in at least three respects, (i) distribution, (ii) heat stability, and (iii) solubility.

Distinction of P-P factor from B₁

Experimental pellagra

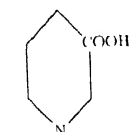
This advance was made possible by the discovery by Goldberger of an experimental condition in dogs, black-tongue, analogous with human pellagra. Since then pellagra has been produced in monkeys (Harris, 1937, c; 1938) and in pigs (Birch, Chick, and Martin, 1937; Chick *et al.*, 1938). The disease in these animals is prevented by the same means as human pellagra. Rats, on the other hand, do not develop symptoms of disease when kept on a diet which will give rise to pellagra in man, dogs, monkeys, or pigs. A condition accepted by Goldberger as being 'rat pellagra' has since been shown to be of a different nature.

Nature of P-P factor

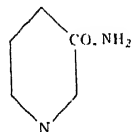
As already mentioned, Birch, György, and Harris in 1935 characterized the P-P factor as a third component of the vitamin B₂ complex (the heat-stable part of vitamin B) different both from this 'rat pellagra' factor and from riboflavin (see p. 574). In 1937 Elvehjem and his collaborators tested nicotinic acid, a substance already known to have a function in at least two intracellular respiratory enzyme systems

upon dogs with pellagra (black-tongue) and found it to be active. Very soon afterwards nicotinic acid was tried in human pellagra by three different groups of investigators and at once met with unqualified success. Nicotinic acid has the simple constitution of β -pyridinecarboxylic acid. The acid amide (a form in which it occurs in nature) is also effective; but many other related substances are inactive.

Chemical constitution of nicotinic acid



Nicotinic acid



Nicotinamide

A suitable curative dose seems to be about 500 mgm. per day given either orally or by injection. An improvement is generally visible within twenty-four hours, and after a day or two any abnormal excretion of porphyrin disappears from the urine. As the patient is likely to be suffering from other concurrent deficiencies, the need for a well balanced nourishing diet deserves to be emphasized. If adequate amounts of protein foods (meat, fish, milk, or cheese) together with fresh fruit or vegetables are included in the diet, pellagra does not occur. The problem is generally an economic one.

Dosage

Prophylaxis

As shown by Goldberger, most protein foods are good sources of the P-P factor. Yeast, fresh or canned salmon, and certain liver extracts are particularly potent. Egg white is probably inactive although it contains abundant riboflavin.

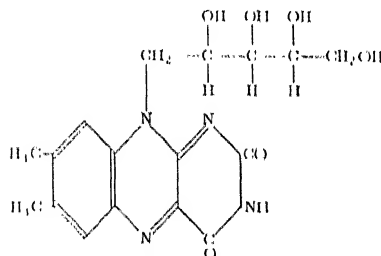
Distribution of P-P factor

(d) Other Components of B_2 Complex

The exact chemical nature of vitamin B_6 (adermin, rat-pellagra factor) is not yet certain but it has been isolated and its hydrochloride has the empirical formula $C_8H_{12}O_3NCl$. Riboflavin (or lactoflavin) is an alloxazine derivative with the following structure:

Vitamin B_6

Riboflavin



Riboflavin

Nothing is known with certainty about the occurrence of a deficiency of these two substances in man; but it has been suggested that some obscure tropical dermatoses may be related to them, and a trial would certainly be worth while in such conditions. György suggested that aerodynia (pink disease, Swift's disease, see Vol. IX, p. 603) may be

Possible human relations of vitamin B_6 and riboflavin

a symptom of lack of vitamin B₆; but here again further work is necessary. It may be noted that in rats deficiency of vitamin B₆ takes the form of a symmetrical dermatitis, attacking particularly the extremities (fore and hind paws, ears, and nose). Riboflavin is needed by rats and by dogs, a deficiency producing in the former an atypical dermatitis and in the latter a condition known as yellow-liver (Sebrell and co-workers, 1937). There is no doubt that it plays an important part as a respiratory enzyme in the mammalian organism. Experimentally in man a deficiency is said to give rise to cheilosis (lesions on the lips and in the angles of the mouth) (Sebrell and Butler).

*Anti-anaemic
extrinsic
factor*

The extrinsic factor of Strauss and Castle has a distribution and a stability to heat resembling that of the vitamin B₂ complex. It is, however, distinct from riboflavin, vitamin B₆, or the P-P factor (Birch, György, and Harris, 1935).

(3)—Vitamin C and Scurvy

(a) *Scurvy: Avitaminosis C*

Early history 1604.] Since the seventeenth century it has been known that scurvy, typified by its characteristic haemorrhages, inflamed gums, and loose teeth, arose from the use of a diet devoid of fresh foods and that it could be cured by raw fruits or greenstuffs. Early records show that the disease was prevalent not only among seamen and armies in the field but among whole populations in northern latitudes, especially during the winter and spring months. By the nineteenth century scurvy was eradicated from the Navy and the Mercantile Marine by the provision of fruit juice.

*Aetiology:
experimental
scurvy*

The proof that scurvy had its origin in the deficiency of a specific vitamin and was not due (as had been supposed) to a bacterial infection, acidosis, or constipation, depended on the production of the disease experimentally in guinea-pigs (Holst and Frölich, 1907 and 1912). Experimental scurvy has been described also in monkeys; but it is of interest to note that dogs, rats, fowls, oxen, pigs, and so far as is known all other species are able to synthesize the vitamin in the body and so can dispense with it from their diet.

Incidence

Scurvy is still endemic in a number of regions, e.g. in the Arctic and among mine-workers in South Africa. During the War 1914–18 outbreaks on a smaller or larger scale occurred among the civilians in every one of the belligerent countries (including the United States and Great Britain), and among the troops at the various fronts there were many thousands of cases. To-day, in the temperate zones, only isolated instances of the definite avitaminosis can be expected, however prevalent a partial deficiency, or hypovitaminosis, may be. But the diagnosis of scurvy is still often missed, because it is not looked for. A not-uncommon cause of the disorder, as mentioned below (p. 586), is a restricted diet given as a result of medical treatment.

*Clinical
picture*

The onset of scurvy is insidious; the picture first is one of general weakness, including pallor, breathlessness, sunken eyes, and a gradual

impairment of appetite and digestion. The temperamental effects were described by Lind (1757) as simulating 'sloth and laziness'. Later there may be pain in the limbs. The two most characteristic symptoms, which take at least four months to develop on a scurvy-producing diet, are (i) swelling of the gums and (ii) multiple haemorrhages; there is also (iii) a secondary anaemia.

In well developed cases in which the haemorrhagic lesions are prominent the diagnosis is usually straightforward, and in doubtful cases, e.g. in which a differential diagnosis from other purpuric disease is needed, a knowledge of the past diet and the rapid improvement when treatment with vitamin C is started often settles the question. Conclusive proof of a scorbutic state can be obtained from a chemical examination of the urine (see p. 584).

Scurvy in infants was long given the misnomer scurvy-rickets, and it was not until 1883 that the error was pointed out by Barlow—hence the additional synonym Barlow's disease. There is no lack of statistics, dating from the end of last century, emphasizing its correlation with the use of sterilized or proprietary foods. As pointed out by Harris and Ray (1935), specimens even of fresh cows' milk have only one-third or one-quarter of the antiscorbutic activity of human milk, and by the time they have been pasteurized, left standing, and again heated, little even of this may be left. For more than a decade it has been the orthodox teaching that the bottle should be supplemented with orange juice; but it is surprising how many mothers do not think it necessary to follow the advice of the welfare centre on this point.

*Diagnosis**Infantile
scurvy**Clinical
features of
infantile
scurvy**Vitamin C
therapy**Prophylaxis**Vitamin C
treatment in
absence of
scurvy*

Diagnosis in acute infantile scurvy may be based on: (i) tenderness in the lower limbs, (ii) subperiosteal haemorrhage with swelling near the lower end of the femur, (iii) radiological appearance of the long bone showing cessation of osteogenesis (Bromer, 1928), (iv) chemical analysis of urine in saturation tests (see p. 584), and (v) knowledge of past diet and rapidity of cure with vitamin C. The period of development is about eight months, and most cases are seen between the ages of 6 and 18 months. The clinical picture, both in adult and infantile scurvy, is discussed more fully under the title SCURVY (see Vol. XI, p. 49).

The treatment for scurvy is a diet enriched with vitamin C, either in the form of orange juice, or preferably large doses of ascorbic acid. For an adult 700 mgm. per day of the crystalline material may be given and for an infant 20 to 40 mgm. has been found adequate. An improvement can generally be detected in 24 to 48 hours and the cure may be complete within about 2 to 3 weeks. For prophylaxis an orange each day, or its equivalent, is sufficient for an adult. An infant receives about 30 to 50 mgm. of ascorbic acid daily in average human milk (Harris and Ray, 1935) and this figure gives a basis for calculation of normal needs.

Treatment with vitamin C has been recommended for a number of haemorrhagic conditions other than scurvy, but there is no evidence

that it is effective. In infectious diseases, however, the need for the vitamin is increased, and special provision of it should be made (cf. below and p. 585).

(b) Vitamin-C Requirements: Hypovitaminosis C and its Detection

*Supposed
symptoms of
sub-scurvy
or latent
scurvy*

For many years it has been maintained by a number of paediatricians that incipient, latent, or subacute scurvy in infants is relatively common but often escapes diagnosis or is mistaken for rheumatism (Hess, 1916, 1920; Comby, 1921). A difficulty was that the symptoms were described as vague: the child was sallow and fretful but not wasted. Provision of additional antiscorbutic food was said to lead to improved stamina and growth and lessened irritability. Similar suggestions have been made about a condition of sub-scurvy in adults (Stefánsson, 1918; Sherman, 1927; Abs, 1928), and also in experimental animals (Meyer and McCormick, 1928). Recently it has become possible to examine the question on a more qualitative basis. This involves the determination of vitamin requirements and tests of the level of nutrition.

*Daily
requirement*

The physiological minimum for an adult is believed to be about 25 mgm. of ascorbic acid daily; this figure has been arrived at in two ways. (i) It is the equivalent of the amount of lemon juice which had been found to be necessary to counteract incipient symptoms of scurvy, according to some old observation in the Navy. (ii) It is the daily dose needed to restore to normal and to keep normal a diminished capillary resistance, arising as a result of a shortage of vitamin C (Göthlin, 1934). With hard physical effort the need for the vitamin is increased as it is also during pregnancy and lactation. In fever again there is an increased demand (see Harris, 1937, a). Children probably require about twice as much as adults per unit of body weight.

Special needs

*Detection of
hypo-
vitaminosis*

Two methods are available for assessing the level of nutrition of the subject with regard to vitamin C. The first depends on a measurement of capillary fragility and the second on an analysis of urine or other body fluids.

*Göthlin
method*

The capillary-fragility test, as described by Göthlin (1933, 1937) and Dalldorff (1934) has the disadvantage that it is only able to detect a fairly advanced or established state of deficiency. The further criticism that an increased capillary fragility is not pathognomonic for scurvy is less cogent, provided it can be shown that the patient has his resistance restored to normal after treatment with vitamin C. The latter procedure, however, is not always feasible, and as a Göthlin test cannot be repeated on the same subject more often than about once in ten days, the practical possibilities of the method are unfortunately somewhat restricted.

*Urine
(saturation)
test for
hypo-
vitaminosis*

The urine (saturation) test for hypovitaminosis involves the measurement of the amount of vitamin C excreted in the urine both before and after a series of test-doses. The greater the deficit in the past intake, the smaller will be the excretion and the greater the number of daily

test-doses needed to bring about a state of saturation, i.e. to give rise to continuous large overflow into the urine. In cases of well developed scurvy no response may be seen for many days, until a total of perhaps 7 to 14 grams of ascorbic acid have been given in the test-doses. Intermediate degrees of deficiency show intermediate responses.

As to normal standards, it has been found that subjects receiving the minimal optimal requirement of 25 mgm. per day referred to above excrete at a level of not less than about 13 mgm. per day (titration with 2:6-dichlorophenolindophenol, calculated as free ascorbic acid) and show good responses to standard test-doses (700 mgm. per 10 stone of body weight) generally on the first and certainly on the second day of test. Hence it is legitimate to conclude that if the response is less than this some degree of subnormality is present. (For details of these quantitative aspects and description of technique see Abbasy, Harris, Ray, and Marrack, 1935; Abbasy, Harris, and Hill, 1937; and Harris and Abbasy, 1937.) For any given intake the excretion is decreased in infectious diseases, notably so in pulmonary tuberculosis (Abbasy, Harris, and Ellman, 1937). An estimate of the level of nutrition can also be gained from tests on blood or cerebrospinal fluid, but the procedures are less simple and have not come into such wide use as the urinary tests.

Standard of normality

Diminished excretion in infection

Other tests

Surveys on subjects of the voluntary hospital class in Great Britain, e.g. at Cambridge, London, and Wolverhampton, show that as many as 70 per cent of them may be below standard judged by the urinary excretion test (see Harris, Abbasy, Yudkin, and Kelly, 1936; Dyke, 1937). Control subjects at institutions, schools, convalescent homes, and elsewhere, who have received their reputed requirements of the vitamin, have been above standard and so have professional and middle-class people who take fresh fruit regularly. Such a high incidence of subnormality may perhaps be surprising, but it must be recalled that, as the surveys of Orr (1936) have shown, more than half the population in Great Britain does in fact receive less than the reputed optimal allowance of vitamin C'. In countries where the intake of fresh fruit is more adequate, the values in the excretion test are correspondingly higher and subnormality seems rarer e.g. in Holland, among city workers in Sweden (Eckelen and Wolff, 1936; Euler and Malmberg, 1935), and in Palestine. It need not be supposed that all individuals who are below standard necessarily show any clearly recognizable clinical symptoms any more than do women or children who, on laboratory examination, are found to have some degree of nutritional anaemia. But there is reason to believe that, in both instances, better health results if the deficiencies are made good.

Prevalence of hypo-vitaminosis C

In examining the vitamin reserves of subjects of the voluntary-hospital class, Harris, Abbasy, Yudkin, and Kelly (1936) were struck by the fact that a disproportionate number of those found to be subnormal were sufferers from gastric and duodenal ulcers, or patients kept for other reasons on 'gastric diets'. They emphasized the need of supplementing

Scurvy in patients on restricted diets

these diets with vitamin C. The absence of the vitamin constituted a vicious circle as it was in itself calculated to delay the healing process. Archer and Graham in 1936 examined 9 patients with gastric and duodenal ulcer and found 6 out of the 9 'were in the sub-scurvy state'. Platt (1936) recorded 4 cases of developed scurvy which had resulted from the prolonged use of 'gastric diets'—'the correct diagnosis had not been made in any of these cases, simply because it had not been considered'. Other examples of frank scurvy caused apparently by the use of 'dyspepsia diets' have been reported by six or seven recent writers. (See also PEPTIC ULCER, Vol. IX, p. 520, and SCURVY, Vol. XI, p. 53.) In many hospitals 'it is still customary to give little or no fresh fruit, the patient being sometimes left to rely for fresh fruit on gifts brought in by his friends and relatives, and it is difficult to avoid the conclusion that there is a real danger that the diet may contain less than the reputed optimum dose of vitamin C' (Harris *et al.*, 1936).

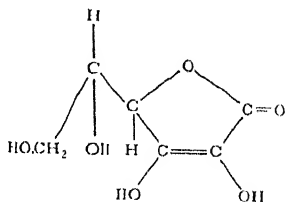
*Defects of
hospital diets*

(c) *Properties of Vitamin C*

Identification One of the earliest systematic attempts to isolate vitamin C was made by Zilva (1924), who succeeded in effecting a 300-fold concentration. In 1932 Tillmans and Hirsch at Frankfurt noticed that the reputed antiscorbutic activity of a number of natural products was roughly parallel with the presence of a reducing principle, which they suggested might be identical with the so-called hexuronic acid previously isolated by Szent-Györgyi in 1928 from adrenal cortex and cabbage. A little later King in America announced the isolation of crystalline vitamin C from orange juice and stated that it had the properties of hexuronic acid, and almost simultaneously Svrbely and Szent-Györgyi in Hungary tested hexuronic acid on guinea-pigs and found it to be active. This identification was at first disputed, but it could be shown that there was an unvarying correlation between hexuronic acid and the presence of antiscorbutic properties (Harris and Ray, 1933, b) and all doubt was set at rest when soon afterwards hexuronic acid was synthesized and shown to be active (Ault *et al.*); in 1933 the more fitting name ascorbic acid was introduced (Szent-Györgyi and Haworth).

*Chemical
properties*

The biologically active form is *L*-ascorbic acid, the structural formula for which is shown below; *D*-ascorbic acid, like a number of other related products, is inactive. *L*-Ascorbic acid is now manufactured on a large scale from sorbose and has acquired a considerable clinical use,



L-Ascorbic acid, vitamin C

being actually cheaper unit for unit than orange juice. From a practical standpoint, perhaps its most important property is its great instability and liability to destruction by oxidation. This inactivation is greatly accelerated by heat and alkali and by the presence of copper, which acts as a catalyst. Under certain mild conditions of oxidation ascorbic acid can be reversibly transformed to dehydroascorbic acid, which is still active; otherwise the activity is lost irreversibly. Unlike vitamin B₁, vitamin C cannot be adsorbed on fullers' earth or charcoal. It dissolves readily in water and methyl or ethyl alcohol but not in fat-solvents.

The best natural sources of the vitamin include the following (figures in brackets are typical ranges of values for the ascorbic acid content in mgm. per 100 g.). Orange juice (50-70), lemon juice (40-60), tomato juice (20-30), pineapple juice (30), and strawberries (50-60). Many green vegetables are highly active, including fresh spinach (30-60), cabbage (30-60), fresh green peas (20-30), turnips (20-40), and green leaves generally. Szent-Györgyi in 1933 discovered that paprika is exceptionally potent; and as Olliver (1936) has shown the same is true of black currants (values about 200 mgm. per 100 g.; cf. also papaya, 50-100; guava, 50-100). Fresh meat contains appreciable quantities of the vitamin. Most ageing and drying processes entail a considerable or complete loss of activity. Canned fruits and vegetables vary considerably in activity, canned tomatoes providing an example of a good anti-scorbutic agent. In commercial pasteurization of milk the presence of copper in the machinery may be responsible for the destruction of the vitamin. Vitamin C appears when seeds germinate (Fürst, 1912), and this principle has been put to practical use in furnishing a supply of antiscorbutic food on expeditions and campaigns. A number of foods which are rich in vitamin B₁, including yeast, yolk of egg, and cereals, are entirely devoid of vitamin C. For full lists of ascorbic acid contents of foods see Füssen and Rosecoe, 1938.

The standard method of estimating vitamin C in foodstuffs was for a long time that introduced by Holst, namely, a determination of the minimal dose needed to prevent typical signs of scurvy in guinea-pigs. A more sensitive method is based on the microscopical examination of tooth structure (Höjer, 1924, 1926; Key and Elphick, 1931). Tillmans observed that many active foodstuffs reduced the dye-stuff 2:6-dichlorophenolindophenol and, by the introduction of a preliminary extraction process and carrying out the titration rapidly in acid solution, Harris and Ray (1933, a) made this the basis for a more specific quantitative method of chemical estimation (see Birch, Harris, and Ray, 1933; Harris, 1937, b).

It is supposed that the action of vitamin C must be linked up in some way with its intense reducing action, which is associated with the presence of the characteristic enolic grouping, $\text{C}(\text{OH}) \text{C}(\text{OH})$. Fish and Harris (1934) found that cells, such as osteoblasts, odontoblasts, and ameloblasts, lose their normal function in the absence of

vitamin C, and they believed that the manifestations of scurvy are due to a loss of activity on the part of the formative cells. Another hypothesis propounded by Wolbach and Howe (1926) is that vitamin C is needed for the production of intercellular substances (see recent discussion by Ham and Elliott, 1938).

*Vitamin C
and infection*

One effect of deficiency of vitamin C, certainly in guinea-pigs, is an increased susceptibility to infection. There is a wide-spread impression that the same is true of human beings. Opinion is still rather divided as to how far vitamin C has an influence on immunity reactions (for discussion see Harris, 1937, a).

5.—FAT-SOLUBLE VITAMINS

(1)—Vitamin D and Rickets

1605.] The clinical care of rickets is discussed fully under the title RICKETS (see Vol. X, p. 671), and the present object is rather to emphasize the main underlying theoretical considerations and to summarize some of the more salient points.

(a) *Rickets and Allied Disorders*

*Recognition
of the
antirachitic
vitamin
Incidence*

As mentioned on page 572 Hopkins in 1906 alluded to rickets as a disease 'in which for long years we have had knowledge of a dietetic factor', and in 1912 Funk postulated that rickets was one of the 'vitamine'-deficiency diseases. Conclusive proof of the existence of an antirickets vitamin was first given when Mellanby (1918) showed that experimental rickets in dogs could be prevented by the use of certain fats in the diet, whereas others were inert. Soon afterwards followed the production of rickets in rats (McCollum *et al.*, 1921; Sherman and Pappenheimer, 1921) and the differentiation of the antirickets vitamin, then to be re-named 'vitamin D', from vitamin A (McCollum *et al.*, 1922).

*Rickets and
sunlight*

It has long been recognized (Palm, 1890) that rickets is most prevalent in the temperate zone or wherever the sunlight is deficient, e.g. in humid climates, in smoky or overcrowded industrial areas, or where the rite of purdah is observed. The influence of sunlight is apparent also in the seasonal variation and in the greater susceptibility of more deeply pigmented peoples, the so-called 'racial factor'. Not until 1924 was the explanation forthcoming of this action of the sunlight—namely, that ultra-violet rays falling on the exposed parts of the body are able to activate the pro-vitamin and convert it into the vitamin.

*Prevalence
of mild
rickets*

With the growth of knowledge and the spread of the infant-welfare movement rickets is becoming less common, and the very severe cases once so familiar are now comparatively rare. But it has been emphasized that after the winter months and in the absence of preventive treatment some degree of rickets is almost inevitable among infants in such climates as those of Britain or many parts of North America

(Gebhart, 1924; J. H. Hess *et al.*, 1930). Such preventive treatment is often neglected and recent surveys, in which the modern more sensitive methods of diagnosis have been used, have in fact indicated that the incidence of mild rickets is still surprisingly high (Newman, 1929; Eliot, 1925, 1926; Crawford and Williamson, 1930).

The underlying lesion in rickets is a deficient calcification of the bones, particularly manifested in the newly-forming bone at the epiphysis, where the zone of provisional calcification is increased in breadth and inadequately mineralized. An irregular growth of the soft osteoid tissue follows, and a consequent swelling of the epiphysal junction ('rachitic metaphysis'). The bending of the inadequately calcified bones and the overgrowth of osteoid tissue causes the well recognized deformities—bow-legs, knock-knees, rachitic pelvis, 'green-stick' fractures, the enlargement of the ends of the bones, and the beading of the ribs. (See also RICKETS, Vol. X, p. 666, especially Plate X, facing p. 669.)

The immediate cause of the deficient calcification of the bone in rickets is thought to be the low level of the phosphate in the blood, or more correctly the low $\text{Ca} \times \text{P}$ product (Iversen and Lenstrup, 1919; Howland and Kramer, 1921, 1922, 1923). Ultimately this chemical defect in the blood is related to an inadequate 'net absorption' (see p. 591) of the P and/or Ca from the intestine. A low blood P (or $\text{Ca} \times \text{P}$ product) is characteristic of active rickets. In fact an analysis of the blood, either for P and Ca or for blood-phosphatase (see Smith, 1933), is the only certain method of detecting incipient rickets or mild rickets. The radiographic abnormalities at the epiphyses do not become apparent until a later stage, but they form the most useful guide in following the course of healing.

From what has been said it will be clear that two factors may be concerned in the causation of rickets—(i) the consumption of a diet deficient in vitamin D, and (ii) lack of exposure to sunlight, the ultra-violet rays of which are able to generate the vitamin in the body. A contributing factor may be a lack of adequate phosphorus or calcium in the diet, absolute or relative, or a low 'availability' of the phosphorus (as in the organically combined form of phosphorus in cereals: phytin, inositol-phosphoric acid (see Bruce and Callow, 1934). E. Mellanby (1937) has suggested that cereals contain an anticalcifying factor, anti-vitamin, or 'toxamin'. In experimental animals at least, other conditions in addition may intensify the severity of rickets, including an increased alkalinity, or base-acid ratio of the diet, which serve to diminish the availability of the Ca and P.

It is evident that if rickets is to be prevented, in northern climates at least, the infant's diet should be supplemented with vitamin D. This may be either in the form of cod-liver oil, or better halibut-liver oil or calciferol (crystalline 'vitamin D₂'). Perhaps the most convenient procedure is to employ an infant food (e.g. dried-milk preparation) in which a standardized amount of vitamin D has been incorporated.

Success has also attended the use of irradiated milk or of helio- or actino-therapy, but these measures are not generally so suitable.

In curative treatment, halibut-liver oil and calciferol have the advantage over cod-liver oil that they can be tolerated at a more adequate level of antirachitic activity. The optimal prophylactic dose for infants and children has been found to be from 500 to 1,500 I.U. daily, and the optimal curative dose about 1,000 to 3,000. The minimal toxic dose is approximately 10,000 I.U. daily. It is important that the correct dosage should be adhered to: the lower limit of toxicity is not far removed from the optimal level for most effective curative treatment (see Harris, 1933).

*Vitamin D
and the teeth*

It has been known since the last century, at least, that rickets is often associated with dental caries, and it is now appreciated that vitamin D, by promoting the normal calcification of the teeth, aids them to resist erosion. Clinical trials have proved that administration of vitamin D is one of the factors which can keep in check the spread of caries (M. Mellanby, 1934).

(b) Vitamin D for Mothers

*In pregnancy
and lactation*

The requirement of nursing and expectant mothers for vitamin D is increased, and an allowance of about 2,000 I.U. daily may be recommended. The need is not so much for any effect that the vitamin may have on the offspring, or on the milk, which is small in ordinary circumstances, but in order to increase the mother's assimilation of calcium and phosphate so as to make good that lost to the foetus or in the milk.

(c) Infantile Tetany, 'Coeliac Rickets', Juvenile Rickets, Osteomalacia, 'Renal Rickets'

*Infantile
tetany*

Infantile tetany is a nutritional disorder. It is seen in association with rickets and its direct cause is hypocalcaemia. It is cured and prevented by the same treatment as rickets. The view that tetany is due to 'mal-function of the parathyroid gland', or to 'intoxication with guanidine', certainly does not apply to true infantile (nutritional) tetany. In fact, treatment by parathormone, which has sometimes been recommended, would seem to be inadvisable except as an emergency measure for it merely aggravates the underlying metabolic error, causing loss of calcium from the body by taking it from the bones.

*Coeliac
rickets*

Failure to assimilate fat in coeliac disease sometimes leads to rickets. This complication can be prevented by the administration of calciferol in a non-fatty medium (Parsons, 1927, 1931).

*Late
(juvenile)
rickets*

In western countries adolescent or juvenile rickets is rare, in contrast with infantile or true rickets. The latter, in its active form, occurs nearly always between the age limits of about six months to two years. In Central Europe at the close of the World War, however, juvenile rickets was prevalent (Simon, 1921). It is still common in a number of eastern countries including India (see e.g. Hutchison and Stapleton, 1924; Wilson, 1931) and elsewhere, for example, among Finns and Laplanders (Kloster, 1931).

Adult rickets is prevalent in a number of eastern countries, e.g. in Northern China (Maxwell and Miles, 1925) and in parts of India (Vaughan, 1929; Wilson and Surie, 1930). Its cause commonly lies in a combination of circumstances; there may be a lack of vitamin D from the diet or diminished exposure to sunlight, as when purdah is observed; but often also there is an actual shortage of calcium or phosphate in the diet. The disease is most commonly associated with pregnancy and lactation, being accentuated by the additional mineral loss which then occurs. The pathogenesis of osteomalacia is the same as of rickets and it yields to the same prophylactic and curative treatment. *Osteomalacia (adult rickets)*

Renal rickets, characterized by a high level of phosphate and a low level of calcium in the blood, appears to have its origin in a renal abnormality which causes a defective urinary excretion of phosphate. It is therefore not, strictly speaking, a nutritional disorder. (See also article RICKETS, Vol. X, p. 672.) *Renal rickets*

(d) *Mode of Action of Vitamin D*

As was hinted above, a deficiency of vitamin D causes an excessive faecal excretion of phosphate or calcium or both. Administration of vitamin D rectifies the error. This may mean that the vitamin causes either an increased absorption from the intestine or alternatively a diminished re-excretion into the alimentary tract. It is not certain which of the two processes is more important, and so the action of vitamin D may be expressed by saying that it causes an increased 'net-absorption' (Harris, 1932). This increased net-absorption is reflected in a raised concentration of phosphate or calcium or both in the blood-stream (Iversen and Lenstrup, 1919; Howland and Kramer, 1921). This in turn promotes an increased calcification of the bone; in other words the defective calcification arises directly from the low blood-phosphorus or calcium. In this sense rickets is a disorder not of the bone but of the blood. In fact it has been shown that bone will calcify normally provided the blood-serum with which it is in contact contains adequate phosphorus and calcium (Shipley, 1924). *Excretion of phosphorus and calcium*

This concept of the mode of action has been substantiated by observations on the effects of excessive doses of the vitamin. It has been shown that just as deficiency of vitamin D causes a low blood-phosphorus and/or calcium and consequent deficient calcification, so an excess of vitamin D brings about an excessive increase in the blood-phosphorus and/or calcium and hence over-calcification (see Harris, 1932). *Hyper-vitaminosis D*

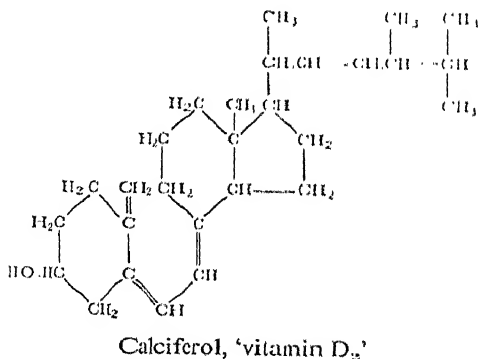
There is as yet no evidence whether or not the vitamin acts directly upon the function of the alimentary canal. It is true that in certain circumstances administration of the vitamin can diminish the alkalinity of the intestinal contents (Zucker and Matzner, 1923). This makes the calcium and phosphorus more soluble and would account for the increased absorption. But this action does not seem to be general, and in any event it lacks explanation.

(e) *Vitamin D and its Properties*

Vitamin D has the most limited distribution of any of the vitamins and this explains why special prophylactic measures are so essential. Halibut-liver oil and cod-liver oil and several other fish-liver oils and fish-body oils are extremely rich sources. Yolk of egg is probably the only common food known to contain it in significant amounts.

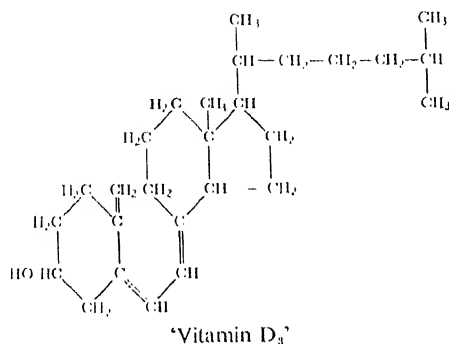
The development of knowledge about vitamin D was made possible by the production of experimental rickets in dogs and rats. In the dog a diet deficient in vitamin D is sufficient to produce experimental rickets (E. Mellanby, 1918), whereas in the rat it is necessary to upset also the Ca/P balance of the diet (McCollum *et al.*, 1921; Sherman *et al.*, 1921).

The first antirachitic factor to be isolated in crystalline form was vitamin D₂ or calciferol, a product obtained by the irradiation of ergosterol. In outline the successive steps leading to this achievement may be summarized as follows: (i) The cure of rickets by actinotherapy (Huldschinsky, 1919), or by irradiation of foodstuffs (Hess and Weinstock, 1924; Steenbock and Black, 1924) or of crude cholesterol (Rosenheim and Webster, 1925; Hess and Weinstock, 1925; Steenbock and Black, 1925); (ii) the identification of ergosterol as the pro-vitamin in the crude cholesterol (Rosenheim and Webster, 1927; Windaus and Hess, 1927); and (iii) the isolation of the vitamin from the irradiation product of ergosterol (Askew *et al.*, 1931; Windaus, 1931). The pure vitamin is no less than 400,000 times as active as cod-liver oil, and one ounce of it would provide a sufficient antirachitic supplement for one day for more than one million children. It cures rats at the level of 1/100,000 mgm. daily or less. It is soluble in the usual fat-solvents and is relatively stable to heat, compared for example with vitamin C or B₁. It has a characteristic ultra-violet absorption spectrum which is used in assaying pharmaceutical preparations. Its structural formula is shown below.



It is only since 1933 that it has been realized that the 'natural' vitamin D ('vitamin D₃') which occurs in cod-liver oil is slightly different in structure from the so-called 'synthetic' vitamin D ('vitamin D₂'),

prepared by irradiating ergosterol. It has been shown that the vitamin in cod-liver oil is identical with a substance which can be obtained by irradiating 7-dehydrocholesterol (cholestadien-3-ol). Weight for weight, calciferol and 'vitamin D₃' are equally active for human beings and for rats, but for chicks the former has only a fraction of the activity of the latter.



Various other forms of vitamin D have been described, but the matter is of more academic than practical interest. Probably 'vitamin D₂' (calciferol) occurs naturally in irradiated vegetable tissues, and vitamin D₃ in most fish oils.

For the assay of vitamin D various alternative procedures are available. The most satisfactory are the following: (i) curative tests on rats with X-ray examination of the rachitic metaphyses, probably the most accurate method (see Bourdillon *et al.*, 1931); (ii) the line test (McCollum *et al.*, 1922), similar to the foregoing but involving a histological instead of an X-ray examination of the bone; and (iii) determination of the ash content of the bones. Assay

(2)—Vitamin A

1606.] From the earliest times it has been known that two disorders of the eye, night-blindness and xerophthalmia, were associated with a fault in the supply of fat in the diet. The error in question gradually came to be linked more specifically with 'fat-soluble' A, later to be known as vitamin A. In 1922 vitamin A was differentiated from the antirachitic factor, vitamin D (see p. 574). History

(a) The Lesions of Vitamin-A Deficiency

In experimental animals a lack of vitamin A leads to some or all of the abnormalities listed in Table III (see p. 594). Experimental avitaminosis A

The abnormalities are given in approximately the order of their appearance, the night-blindness being an early sign and the nerve degeneration, for example, a later or at any rate a chronic one. Most of the ill effects, e.g. numbers 4, 5, 6, 7, and 8 (i.e. infections, xerophthalmia, calculi, periodontal changes, and reproductive failure) can probably be attributed to number 3, i.e. to the xerosis or keratinization of membrane tissue. Xerosis as an essential lesion

TABLE III.—Effects of Vitamin-A Deficiency

ABNORMALITY	LITERATURE REFERENCE
1. Night-blindness	Holm, 1925.
2. Failure of growth	McCollum and Davis, 1913; Osborne and Mendel, 1913.
3. Metaplasia (xerosis) of epithelial tissues	Mori, 1922; Wolbach and Howe, 1925.
4. Multiple secondary infections	McCollum, 1917; Drummond, 1918; E. Mellanby, 1919.
5. Xerophthalmia and keratomalacia	Osborne and Mendel, 1913, 1914, 1915.
6. Renal calculi	Osborne and Mendel, 1917.
7. Periodontal hyperplasia	M. Mellanby, 1930.
8. Reproductive failure	Drummond, 1918.
9. Degenerative changes in central or peripheral nervous system	Hughes <i>et al.</i> , 1929; E. Mellanby, 1930.

*Vitamin A
and infection*

The infections in particular seem to be a direct result (Harris, Innes, and Griffith, 1932) of the structural break-down of the epithelial tissues, which permits the accumulation thereon and invasion by chance organisms which would normally be non-pathogenic. Vitamin A does not appear to influence immunity reactions, and has generally given disappointing results when tried in the treatment of common infective diseases or as a prophylactic measure against ordinary respiratory infections (Wright *et al.*, 1931; Barenberg and Lewis, 1932; Orenstein, 1932; MacKay, 1934).

(b) Incidence of the Various Forms of Vitamin-A Deficiency

The occurrence of vitamin-A deficiency has been recognized in different parts of the world by widely differing symptoms and it will be most convenient to consider the more important of these separately. It is not yet known for certain whether lack of vitamin A in human beings may give rise to the abnormalities classed above as numbers 6, 7, 8, and 9 among those produced in experimental animals (i.e. calculi, periodontal changes, reproductive failure, and degeneration of nerves). Numbers 1 to 5 on the other hand (night-blindness, growth failure, xerotic manifestations, multiple infections, and xerophthalmia or keratomalacia) have all been seen in man as a consequence of the deficiency.

*'Dark-adaptation'
tests
(incipient
night-blindness)*

The most sensitive known method for detecting the mildest degree of hypovitaminosis A is by a test for dark adaptation. This test depends on the fact that the visual purple in the retina of the eye is a derivative of vitamin A; when the body's supplies of the vitamin are below the optimum a diminished visual acuity results, which can be demonstrated by tests carried out in a dim light after exposure of the subject to brilliant illumination. The procedure needs careful control

in order to check irregularities due to normal fluctuations and variations as well as to the possibility of the individual under test showing an improved performance with increasing familiarity with the instrument. Surveys in Great Britain, in which such sources of error were guarded against, showed that about one-third of the poor elementary-school children examined in London and Cambridge were subnormal, whereas better-fed, public-school boys and children in institutions where adequate supplies of vitamin A were habitually given were nearly all normal (Maitra and Harris, 1937; Abbasy and Harris, 1938). This finding corroborates the budgetary surveys of Orr (1936) according to which a large proportion of the population were judged to have intakes of vitamin A below the reputed optimum. In America (O'Brien, 1933; Jeans and Zentmire, 1934) and in other industrial countries of the West very similar conditions appear to apply, and in parts of India (see Aykroyd and Krishnan, 1936) and in other oriental regions conditions are no doubt far worse.

Definite subjective symptoms of night-blindness, such as obtrude themselves on the patient, deserve to be clearly distinguished from the earlier and milder manifestation of sub-normal dark adaptation which, as has been shown, may need special laboratory equipment for its detection. From records in the literature it is clear that this mark of more advanced deficiency has been common in a number of parts of the globe, e.g. Newfoundland (Little, 1912; Aykroyd, 1930), Labrador (Little, 1912), China (Pillat, 1929; Chou, 1930), Guatemala (Macphail, 1929), and the Dutch East Indies (Wille, 1922). Aykroyd and others have made the interesting observation that when the organism has absorbed a large dose of vitamin A the sight may be restored to normal within so short a time as 12 to 24 hours.

One of the earliest of the clinical signs of deficiency of vitamin A is a characteristic appearance of the skin first described by Loewenthal in Uganda, and later by Nicholls in Ceylon who gave to it the name 'phrynoderma' (from the native 'toad skin'). Loewenthal described it as consisting of a dryness of the skin with a keratinized papular eruption, originating at the pilo-sebaceous follicles and occurring on most parts of the body except the face. This condition has been shown to be very common in Ceylon (Nicholls, 1933, 1934), in Uganda (Loewenthal, 1933; Mitchell, 1933; Wright, 1930), and in China (Pillat, 1929; Frazier and Hu, 1931). In England MacKay (1934) considered that among infants, minor infections of the skin constitute a common result of hypovitaminosis-A.

Whereas in adults a long-continued deficiency of vitamin A generally gives rise to night-blindness, in children xerophthalmia, with or without keratomalacia, is the more usual symptom. The classical accounts are those given by Mori in Japan (1904) and by Bloch in Denmark (1917, 1924). In India xerophthalmia is so common that it is said to be the principal cause of blindness (Wright, 1931; Kirwan, 1931); other records refer to its prevalence in Ceylon (Nicholls), parts of China

(Pillat and Chang, 1932), in Yucatan (where one child in every five was a victim; Carrillo, 1932), in Malaya, in Newfoundland, and elsewhere.

(c) Quantitative Requirements

Needs of adults

Probably about 3,000 International Units of vitamin A are needed daily by the average adult. 'Such a supply is afforded by a daily intake, for example, of 500 millilitres [$\frac{7}{8}$ of a pint] of whole fluid milk, one egg, 25 grammes [$\frac{9}{10}$ ounce] of butter and a medium-sized serving of a green leafy vegetable' (*League of Nations, Bulletin of Health Organization*,

Mothers

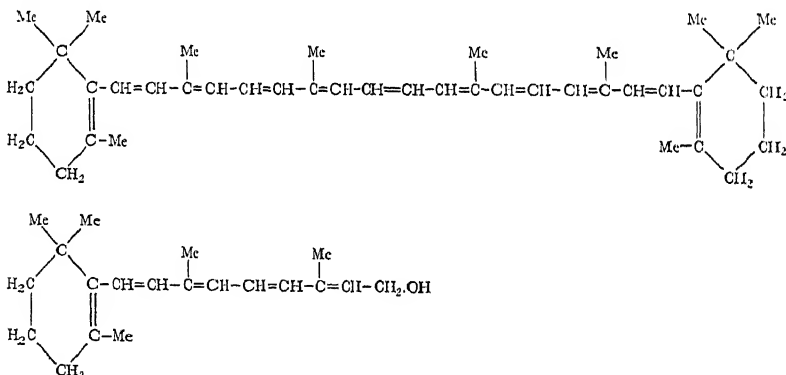
Infants and children

1938). For pregnant and lactating women the needs are increased. The requirement of infants and growing children is greater than that for adults, weight for weight. The vitamin may be supplied to infants in the form of a fish-liver oil or a concentrate.

(d) Properties of Vitamin A

Identification

Observations by Steenbock (1919), Euler *et al.* (1928), and Moore (1929) led to the recognition that two distinct substances, the yellow pigment carotene and the 'colourless vitamin A' of liver oils, share vitamin-A activity. Carotene occurs as such in the vegetable kingdom and some or all of it is converted to vitamin A in the animal organism. The chemical relation between β -carotene and vitamin A (Karrer *et al.*, 1931) is shown in the formulae below. It is now known that several other carotinoid substances in addition to β -carotene also possess vitamin-A activity, but these are probably of little practical importance: (β -carotene is the most active form and α -carotene and γ -carotene and also cryptoxanthine have about half the activity).



β -Carotene above, showing its relation to vitamin A, below

Chemical properties

Vitamin A is unstable to heat in the presence of air but is relatively stable if oxidation is excluded (Hopkins, 1920). Substances rich in vitamin A absorb ultra-violet rays in the region of 328 $m\mu$. They also give a brilliant blue colour with antimony trichloride (Carr and Price, 1926). These reactions, and biological tests on rats, are utilized for the assay of the vitamin. The international unit is 0.0006 mgm. of a standard specimen of β -carotene.

In the animal kingdom fish-liver oils and fish-body oils provide the best source of vitamin A. Butter and beef and mutton fats are but moderately active. Ordinary margarine is deficient but specially activated brands can be purchased. *Distribution in animal fats*

Most leafy vegetables are rich in β -carotene and hence highly active. The activity often runs parallel with the degree of greenness. Among root vegetables the carrot and sweet potato are active; most others are poor. Many fruits contain significant quantities. *In vegetables*

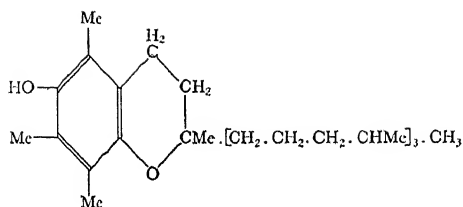
Large amounts of vitamin A can be stored in the liver and serve as a reserve available for use when the diet is deficient. The vitamin can be passed from the mother to the offspring, both through the placenta and in the milk, but the quantity is severely limited by a physiological control (Dann, 1934). *Storage in the body*

(3)—Vitamin E

1607.] In experimental rats the most prominent feature of vitamin-E deficiency is the interruption of pregnancy (the so-called resorption gestation) in the female. Fertilization and implantation take place normally but after about two weeks there is resorption of the foetus, and sterility results. The defect is reversible, that is to say it can be cured when vitamin E is given. In the male there occurs a degeneration of the germ-cells which on the other hand is less readily curable. Other abnormalities which may be seen, particularly in a more chronic state of deficiency, include paralysis and muscular dystrophy. *Experimental avitaminosis E*

Little is known about the effects of a deficiency in other species, although it appears that sterility in cattle may sometimes respond to vitamin E (Vogt-Møller and Bay, 1931). As far as human beings are concerned, there is rather a paucity of properly controlled clinical observations. Nevertheless some recent clinical trials suggest that habitual abortion in women is sometimes amenable to treatment with vitamin E (e.g. Vogt-Møller, 1933, 1936; Tanberg, 1936; Currie, 1936, 1937; Young, 1937). It seems worth while, then, when other more obvious causes of sterility have been ruled out, to make a trial with suitable concentrates of this vitamin. *In clinical medicine*

The usual source of vitamin E is wheat-germ oil. Green leaves also contain it. Cod-liver oil and other fish-liver oils, although so richly endowed with the two other important fat-soluble factors (vitamin A and vitamin D), are generally almost devoid of E. In 1936 Evans and his co-workers isolated the vitamin in a crystalline form and gave it the name α -tocopherol. It has the formula $C_{55}H_{100}O_2$ and is a chroman derivative. It is fairly stable to heat but is destroyed during the development of rancidity in fats. Like vitamin A, but in contrast with vitamins B₁ or C, vitamin E can be stored in the animal organism to a remarkable degree. A second form, β -tocopherol, is somewhat less active. *Properties of vitamin E*
 α -tocopherol

*α*-Tocopherol, vitamin E

6.—OTHER VITAMINS

- New factors* 1608.] Experiments on animals have given indications of the existence of a number of vitamins in addition to the better-known ones so far discussed. With the exception of 'vitamin P' little is known about their chemical structure. Often, too, the pathological effects of the deficiency have not yet been clearly characterized. In only three instances has any specific claim been made for possible uses in clinical medicine.
- Vitamin H* Deficiency of vitamin H in rats gives rise to a seborrhoeic dermatitis which is cured by its administration. György suggested that it should be tried in various seborrhoeic conditions in man and in psoriasis, but favourable reports of its use are still lacking.
- Vitamin P (hesperidin)* Vitamin P ('citrin', 'flavone', hesperidin) is claimed to have a vitamin-C-sparing action in guinea-pigs and to check haemorrhages by diminishing the capillary fragility. The reality of vitamin-P deficiency in guinea-pigs has been questioned (Zilva, 1937); on the other hand several clinical investigators claim that it has been effective in reducing haemorrhages, e.g. in haemorrhagic nephritis and other conditions (Lajos, 1937; Scarborough and Stewart, 1938).
- Vitamin K* In chickens, vitamin-K deficiency is characterized by the occurrence of haemorrhages and a diminished clotting power of the blood, due to a fall in the prothrombin. It is stated by Dam and Glavind (1938) that a low vitamin-K value, as measured by the blood-clotting technique, was found in several cases of obstructive jaundice due to cancer, in which a reduced absorption of the vitamin from the intestine would naturally be expected. Parenteral administration of the vitamin brought the clotting power back to normal. Thus here again possible clinical applications are worth considering for the future.

7.—DIETETICS AND APPLICATIONS

- Infants* 1609.] Fortunately it is possible to formulate a few simple rules which should ensure an adequate supply of vitamins under most conditions. For artificially fed infants a diet based on whole milk modified if necessary and with the addition of iron, supplemented with orange juice or ascorbic acid, and vitamins A and D in the form of a concentrate, should meet all needs. The daily requirements for the various vitamins have already been dealt with, and generally the directions

given with any reputable proprietary preparation can be safely followed. Experience in America suggests that it is probably an advantage to provide a supplement of vitamin B₁ (or B complex) from a fairly early age: this may be given as a cereal (wheat germ) preparation or as a concentrate. See also under titles FOOD (Vol. V, p. 393), and INFANT FEEDING (Vol. VII, pp. 140, 145, 164, 165, and 166).

The commonest faults in the diet of adults are, probably, shortages of vitamins C and B₁, at least under the conditions prevailing in Great Britain. Economic reasons are usually responsible. The 'average middle-class diet' is likely to be satisfactory provided it includes the following daily— $\frac{1}{2}$ to 1 pint of milk (1 to 1 $\frac{1}{2}$ pints for children), one good protein dish, one orange, or the equivalent of vitamin C in the form of other fruit, salad, or vegetables. Vitamin B₁ is likely to be low in the diets of most working-class people, and the simplest way of correcting the error is by the substitution of wholemeal bread for white. For children the most important single measure is to include a pint to a pint and a half of milk daily. During the years of growth the regular use of vitamin D—preferably combined with vitamin A—is to be recommended, especially in winter (for doses see p. 590).

In various parts of the world single or multiple deficiencies present special problems; for example, in the East, polished rice can often with advantage be replaced by parboiled or unpolished rice, and the use of beans and wholemeal cereals may be encouraged. In the far north populations short of vitamin C are being taught to take certain berries; or extracts derived from pine needles or hip berries, or sometimes synthetic preparations of ascorbic acid, are being distributed. In regions where maize is the staple diet the public authorities are instituting measures to combat pellagra. These are but a few examples.

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VITILIGO

See LEUCODERMIA, Vol. VII, p. 705

VOCAL CORDS, DISEASES

See LARYNX DISEASES, Vol. VII, p. 618

VOLVULUS

See ABDOMINAL PAIN AND ACUTE ABDOMINAL
EMERGENCIES, Vol. I, p. 33; and INTESINAL OBSTRUCTION,
Vol. VII, p. 234

VOMITING, CYCLICAL

See ACIDOSIS, Vol. I, pp. 146 and 150; ALLERGY, Vol. I, p. 306;
and MIGRAINE, Vol. VIII, p. 607

VULVA AND VAGINA DISEASES

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Reference may also be made to the following titles:

DYSPAREUNIA	SYPHILIS
GONORRHOEA	URETHRA DISEASES
LEUCORRHOEA AND OTHER	UROGENITAL ORGANS,
NON-HAEMORRHAGIC	ABNORMALITIES
VAGINAL DISCHARGES	

1.—VULVA

(1)—Vulvitis

*Simple
vulvitis*

1610.] Simple vulvitis may be due to various organisms and is found especially in association with uncleanness, when the bacteria may

have been spread from the anus. It may result in papular eczema with purulent discharge and areas of incrustation. It usually clears up with frequent cleaning followed by drying of the vulva and the application of calamine lotion.

Follicular vulvitis occurs on the hair-bearing parts of the vulvar skin; *Follicular* furuncles and boils may develop and require hot antiseptic applications or incision.

Erysipelatous vulvitis is a rare condition in which acute streptococcal *Erysipelatous* inflammation rapidly spreads over the vulva and neighbouring areas, sometimes causing subcutaneous cellulitis and abscess formation. The patient is acutely ill, and the prognosis is often bad. Treatment with sulphanilamide should be begun at once, and the vulva should be painted with a 10 per cent solution of ichthammol in glycerin or a 1 per cent solution of picric acid in water.

Diabetic vulvitis gives a characteristic picture which may often be *Diabetic* recognized at sight. The vulva is swollen and oedematous, and the skin is bright red and covered in places with lightly adherent whitish patches which, on microscopical examination, are found to consist of desquamated epithelial cells, pus, and threads of monilia. The inflammation is mainly due to the fungus, the growth of which is favoured by the continual presence of sugar on the skin. Treatment of the diabetes mellitus will usually cure the vulvitis; sodium bicarbonate douches may be given, or the skin may be painted with a 1 per cent solution of gentian violet. Pessaries of 5 per cent lactic acid in a glyco-gelatin base may give better results in a resistant case, in which the vagina also is infected.

Acute vulvitis is also seen in association with vaginitis due to gonorrhoea, *Trichomonas vaginalis*, *Bact. coli*, and irritating cervical discharges. (See GONORRHOEA, Vol. VI, p. 26; and LEUCORRHOEA AND OTHER NON-HAEMORRHAGIC VAGINAL DISCHARGES, Vol. VII, p. 712.)

(2)—Ulceration

Simple ulceration may be due to trauma or to vulvitis; a granuloma *Simple ulceration* may occur in an unhealed puerperal tear and may persist for a month or two.

The *ulcus vulvae acutum* of Lipschütz is stated to be due to *Ulcus vulvae acutum* *Bacillus crassus*. The ulcers are multiple, round, and shallow, from one-eighth to one-half inch in diameter, with a greyish soft base, and tender to touch. Similar ulcers are often found in the mouth. They may be treated by painting with a 5 per cent solution of silver nitrate or a 10 per cent aqueous solution of mercurochrome; there is a tendency to spontaneous healing when the patient is at rest, but new crops of ulcers are liable to break out.

Diphtheritic and tuberculous ulceration is rare. The organisms may *Diphtheritic and tuberculous* be grown in culture, or identified in smears or by biopsy in the case of tuberculosis. Diphtheritic ulceration should be treated by antitoxin.

Excision, curettage, or cauterization may be employed for tuberculous ulceration.

Noma Gangrenous vulvitis or noma occurs in children during measles and other acute specific fevers, in erysipelas, and in venereal infection. The patient's strength must be maintained and the local lesion treated by excision or cauterization.

Carcinoma Carcinoma must be kept in mind, even in young women, and the diagnosis established by biopsy in any persistent indurated ulcer.

Venereal ulcers For venereal ulcers of the vulva see CHANCROID, Vol. III, p. 97; GONORRHOEA, Vol. VI, p. 26; GRANULOMA, ULCERATIVE, Vol. VI, p. 57; LYMPHOPATHIA VENEREUM, Vol. VIII, p. 297; and SYPHILIS, Vol. XI, p. 573.

(3)—Pruritus Vulvae

Causes This is a common symptom of vulvitis, leucorrhoea, and leucoplakia, but it may occur without any apparent vulvar abnormality apart from lesions produced by scratching. The urine must always be examined for sugar and pus, which may cause irritation. The anal canal should also be inspected because thread-worms or irritant discharges from a fissure or piles may be responsible.

Treatment Any possible cause of the pruritus is treated, and calamine lotion with 1 or 2 per cent phenol is used to relieve the irritation. More severe cases may require analgesic ointments, such as 5 per cent thymol or menthol, 10 per cent cycloform or percainal, or even 5 to 10 per cent cocaine. When the pruritus is a symptom of neurosis, oral administration of bromide and valerian may help. When there are atrophic changes, oestrin therapy is indicated. Stilboestrol may be given in doses of 3 mgm. daily by the mouth for three weeks, the dose then being decreased; or oestradiol benzoate, 50,000 international units by intramuscular injection twice a week for three weeks, followed by 4,000 international units of oestrone daily by the mouth. When skin changes are not present X-ray treatment is usually successful in the worst cases, but the relief may not be permanent. Finally, wide subcutaneous infiltration with 1 per cent solution of procaine hydrochloride (novocain) or 3 per cent benzocaine solution in the form of 'A.B.A.' may be tried. (See also PRURITUS AND PRURIGO (HEBRA), Vol. X. p. 168.)

(4)—Leucoplakia Vulvae

Morbid anatomy Leucoplakia vulvae is a chronic inflammatory condition of unknown aetiology. In the early stages the vulva is red and swollen, the skin becomes thickened, and microscopical section shows congested blood-vessels and round-celled infiltration in the subepithelial tissues. After a time the labia shrink, as fibrosis and retraction take place under the skin, and the piled-up epithelium takes on the white colour which gives the condition its name. In the later stages, desquamation occurs in some areas and cracks and ulcers appear in the indurated skin. Carcinoma may develop in these ulcers. The disease may affect part

or the whole of the vulva, except the vestibule and urethral orifice which are never involved; it sometimes spreads onto the perineum and peri-anal region and the adjacent parts of the thighs.

Pruritus is usually the first symptom, and a burning feeling and pain are complained of later, in the stage of desquamation and ulceration. *Clinical picture*

When pruritus is the only symptom, it should be treated with lotions, ointments, or oestrin preparations, as suggested above (see p. 608). In the stage of hyperkeratosis and ulceration it may be necessary to excise the vulva, especially if carcinomatous change is suspected. When the condition is extensive, excision of the whole area may be difficult or impossible, but vulvectomy usually gives relief. *Treatment*

(5)—Kraurosis Vulvae

Kraurosis vulvae is a condition of extensive vulvar atrophy which sometimes follows the menopause. It is probably due entirely to lack of hormones, especially oestrin, consequent on the menopausal atrophy of the ovaries. The patient complains chiefly of soreness of the vulva; pain on micturition and pruritus are sometimes present and dyspareunia may be the chief symptom in advanced cases. The disease involves the entire vulva including the vestibule. The labia minora, clitoris, and vaginal orifice shrink and the skin becomes very thin and shining, with large yellow and small red areas. *Aetiology*

In mild cases palliative treatment with antipruritic and analgesic lotions and ointments may be tried and oestrin therapy, as for pruritus, is useful. If dyspareunia is an important symptom a plastic operation may be necessary. *Clinical picture* *Treatment*

(6)—Tumours

Fibroma and neurofibroma may occur on the vulva and do not differ from similar growths found elsewhere in the skin (see Vol. IX, p. 216). They usually become pedunculated and are easily removed if they give rise to pain or discomfort. *Fibroma and neurofibroma*

Papillomas are usually of the kind called condylomata acuminata or gonorrhoeal warts. They are, however, not due to gonorrhoea or to the irritation of a profuse vaginal discharge, as is commonly stated, because typical warts are sometimes found in patients who are not infected with gonorrhoea and are free from leucorrhoea. The cause is probably a filter-passing virus. The warts are small, many-pointed, and often pedunculated; they are found on both the moist and the dry areas but rarely inside the vagina. Treatment consists of touching the papillomas with a paint, such as equal parts of tincture of ferric chloride and blistering fluid, or with acid solution of mercuric nitrate. The paint should be carefully mopped off after application, to prevent ulceration of normal areas. *Papilloma* *Aetiology* *Treatment*

Carcinoma is the commonest vulvar tumour. It is usually a disease of elderly women and begins on the labia majora or minora, the clitoris, or the perineum. It is of the squamous-celled type and may follow

leucoplakia. Metastasis occurs in the inguinal glands. In the early stages the patient complains only of a small lump on the vulva; later ulceration occurs and there may be very great pain and tenderness to touch. There is a thin purulent discharge but bleeding is unusual. On examination a hard nodule is found in the skin, or an ulcer with raised rolled-out edges and indurated base. When the disease has followed leucoplakia the growths may be multiple. The labia and the clitoris may be removed by an inner incision around the vaginal orifice and vestibule and an outer incision encircling the entire vulva, leaving a wide margin around the growth. The inguinal glands must always be removed, but not necessarily at the same time, as metastasis does not occur in the intervening lymphatics except in cases in which treatment is hopeless. The incision extends along the line of the inguinal (Poupart's) ligament, inclining downwards at the inner end to enable the glands round the upper part of the saphenous vein to be removed.

Clinical picture

Treatment

Melanoma and sarcoma

Melanoma and sarcoma of the vulva are rare and should be treated by removal of the inguinal glands and vulva in one mass. Radium may be applied to the surface of the primary growth, and the inguinal glands may be treated by X-rays as an alternative to operation in these growths and also in carcinoma. The results have been inferior to those of operation.

(7)—Greater Vestibular (Bartholin's) Gland

Abscess

Abscess of the greater vestibular (Bartholin's) gland is usually due to gonorrhoea but cases in which other organisms are responsible are by no means rare. The abscess should be incised and drained. If it recurs, the gland should be excised in an interval between acute attacks.

Cysts

Cysts of Bartholin's gland most commonly follow infection, but small cysts may occur when the duct has been blocked by a puerperal laceration. They occur at the side of the lower end of the vagina and enlarge outward into the base of the labium minus. If they cause pain or discomfort they should be excised under general anaesthesia and the cavity obliterated by mattress sutures of catgut, which also secure haemostasis. The cyst is usually deep-seated and adequate local anaesthesia is difficult to obtain.

Carcinoma

Carcinoma of Bartholin's gland occurs very rarely in elderly women. It is an adeno-carcinoma and the metastases occur in the inguinal glands. The treatment is wide excision of the enlarged hard gland and removal of the inguinal lymphatic glands.

2.—URETHRA

(1)—Urethritis

Aetiology

1611.] Inflammation of the urethra is generally due to gonorrhoea, but other organisms, such as *Bact. coli*, are occasionally responsible. In acute cases the patient complains of frequent and painful micturition,

and on examination the meatus is seen to be reddened and swollen. In chronic cases there may be no symptoms, but complaint of leucorrhoea due to an accompanying vaginitis is often made. Skene's tubules and similar lacunae inside the urethra may be infected; this may cause recurrence of the urethritis and vaginitis after treatment. The urethra and the Skene's tubules may be thickened and palpable through the anterior vaginal wall and discharge may be expressed from them.

Treatment consists in irrigation of the urethra, as for gonorrhoea, or in applications of 10 per cent solution of mercurochrome or silver proteinate on a probe covered with cotton-wool. When there is persistent infection of Skene's tubules they may be washed out with an antiseptic injected through a blunt needle, or cauterized and opened on the vaginal or urethral aspect with an electric cautery. An abscess of a Skene's tubule is occasionally found and requires incision and drainage. *Treatment*

(2)—Urethral Caruncle

Urethral caruncle is a soft growth arising from the posterior wall of the urethra, just inside the meatus. The aetiology is obscure. It has been stated to be due to chronic infection of Skene's tubules but it most commonly occurs in elderly women who give no history and show no signs of urethral infection. It is often associated with vulvar atrophy and may be of similar origin. *Aetiology*

The growth is usually pedunculated, sometimes sessile, and of a bright cherry-red colour, lying in or projecting from the meatus. On section it is found to be covered with stratified epithelium, processes of which penetrate deeply into the connective-tissue centre, which contains numerous large blood-vessels. *Morbid anatomy*

Symptoms may be absent but most caruncles are very sensitive and cause pain on micturition, and even when the patient walks or sits down. *Clinical picture*

The urethra should be dilated with metal dilators and the caruncle excised with a small area of the urethral wall. The incision is repaired with fine catgut sutures. Cauterization or diathermy are alternative methods of treatment. *Treatment*

(3)—Carcinoma

Carcinoma of the urethra is a rare disease of elderly women. It usually projects as a cauliflower-like mass from the meatus and may originate in Skene's tubules. The symptoms are pain, discharge, and haemorrhage. Adequate removal is difficult and will probably cause incontinence of urine. The best treatment is by radium plaques applied to the growth, but early recurrence is usual.

For injury and prolapse of the urethra see p. 613.

3.—VAGINA

Dyspareunia and vaginismus are dealt with in the article **DYS-PAREUNIA**, Vol. IV, p. 361.

The vaginal flora and factors influencing it are dealt with under the title **LEUCORRHOEA AND OTHER NON-HAEMORRHAGIC VAGINAL DISCHARGES**, Vol. VII, p. 712.

(1)—Vaginitis

Aetiology

1612.] The following causes of vaginitis must be considered in seeking the origin of vaginal inflammation: (i) foreign body, such as a pessary or some object introduced by the patient; (ii) chemical irritation, due to the use of strong antiseptic for douching; (iii) inflammation following the use of a douche which has been given at too high a temperature; (iv) irritation from chronic septic cervical discharges, or pus coming from a pyometra; (v) organisms, such as gonococci, *Trichomonas vaginalis*, *Bact. coli*, streptococci, monilia, and *C. diphtheriae*; and (vi) a senile vagina sensitive to organisms which the vagina can resist before the menopause.

Clinical picture

The only constant symptom is vaginal discharge, but complaints of soreness, pruritus, and burning pain on micturition are often made. The vaginal wall is bright red in acute cases and the discharge is obviously purulent; in chronic cases there may be only slight injection of the vaginal wall.

Treatment

An accurate diagnosis must be made before prescribing treatment. Cultures are necessary, and the discharge should also be examined fresh in saline under the microscope for *Trichomonas vaginalis*. If a pessary is the cause it may be impossible for the patient to continue to wear it, and the symptoms of prolapse must be relieved by operation. Senile vaginitis may be treated by douching with 1 to 2 per cent solution of sodium bicarbonate or 0.5 to 1 per cent solution of lactic acid. Oestrin preparations may be given, as in pruritus (see p. 608), to thicken the epithelium and encourage the growth of Döderlein's bacillus. The treatment of vaginitis due to gonococci, trichomonas, and other organisms will be found in the article on **LEUCORRHOEA** (see Vol. VII, p. 716).

(2)—Ulceration

Vaginal ulceration may be due to a pessary, an infected laceration, friction in a case of prolapse, syphilis, tuberculosis, or carcinoma. It may be necessary to establish the diagnosis by biopsy. The appropriate treatment will be evident when the diagnosis has been established.

(3)—Cysts and Tumours

Cysts

Cysts of the vagina are usually thin-walled swellings on the anterior or lateral walls, more rarely on the posterior wall. They commonly

originate from persistent portions of Gärtner's duct, or occasionally from aberrant mucous glands. If discomfort or dyspareunia are caused, the cyst should be shelled out after incision of the epithelium.

Fibroma, fibromyoma, and fibrosarcoma of the vagina are rare tumours usually found close under the epithelium. They may be mistaken before operation for the more common tense cysts. The tumour can generally be shelled out and should be microscopically examined to find out whether it is malignant. A sarcoma will require subsequent treatment with radium by surface application and deep X-ray therapy.

Carcinoma of the vagina may be secondary to a carcinoma of the cervix or of the body of the uterus. If it spreads from the cervix it will require the same treatment as the primary growth. Carcinoma secondary to a growth in the body of the uterus is commonly found as an isolated nodule near the introitus. It causes a haemorrhagic discharge and may be the first manifestation of the disease. The prognosis is not necessarily grave if the uterus can be removed by total hysterectomy, because there may be no other metastasis than that seen on inspection, and this can be treated by local application of radium. In chorionic carcinoma of the uterus, secondary growths may be found in the vagina (see Vol. III, p. 222) and may be treated by excision or radium. A few cases of primary chorionic carcinoma of the vagina have been recorded.

Primary carcinoma is rarer than secondary. It is squamous in type and may occur on any part of the vaginal wall. It is sometimes due to ulceration from a pessary. The only symptom in early cases is haemorrhagic discharge. The growth is radiosensitive and may be treated by local application of radium. If the primary growth is in the lower third of the vagina, metastasis may occur in the inguinal lymphatic glands.

(4)—Vaginal Fistulae

Urethral, vesical, ureteric, and rectal fistulae may occur from laceration or sloughing during labour, or from injury during an operation. If the urethra is extensively damaged it may be impossible to reconstruct it. A small urethral or vesical fistula may be repaired from the vaginal aspect by thoroughly separating the inner and outer layers of the mucosa and suturing them separately in such a way that broad areas of the raw surface are joined together. Fine catgut should be used for the inner layer of vesical or urethral mucosa, and catgut or silkworm-gut for the vagina. The bladder may be drained by a fine rubber catheter attached to a stitch in the vestibule. With larger fistulae drainage by suprapubic cystostomy is better and it may be necessary to repair the bladder wall through the cystostomy opening, because it can be done more accurately from this aspect. Ureteric fistulae are very difficult to cure and should be approached through the bladder, because re-implantation of the ureter higher up the bladder may be needed.

Recto-vaginal fistulae are usually comparatively easy to cure unless they are in the upper part of the vagina. In the lower vagina the track

of the fistula is generally long, and the perineum and the anterior wall of the anal canal should be incised in order to convert the fistula into a complete tear. The track of the fistula can then be completely excised, and the rectal wall, perineum, and vagina repaired by separate layers of interrupted sutures. Fine catgut is used for all sutures except those on the surface of the perineum, which are of silkworm-gut. A fistula in the middle or upper vagina may be repaired by separation of the two layers of mucosa, and sutures infolding the one layer into the lumen of the rectum and the other into the lumen of the vagina apposing the raw surfaces. Colostomy is never necessary for the cure of a low recto-vaginal fistula, but a fistula in the posterior fornix will probably require laparotomy.

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WARTS

See SKIN DISEASES: TUMOURS, Vol. XI, p. 203

WEBBED FINGERS

See BONE DISEASES, Vol. II, p. 560; and
HAND, DISEASES AND DEFORMITIES, Vol. VI, p. 172

WEIL'S DISEASE

See JAUNDICE, Vol. VII, p. 267

WHIPWORM

See NEMATODE INFECTIONS, Vol. IX, p. 131

WHITLOW

See HAND, DISEASES AND DEFORMITIES, Vol. VI, p. 182; *and*
NAILS, DISEASES OF, Vol. IX, p. 86

WHOOPIING-COUGH

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1.—DEFINITION

(*Synonym.*—Pertussis)

1613.] Whooping-cough is a specific infective disease deriving its name from its main symptoms, a paroxysm of short coughs followed by a crowing inspiration. The disease is essentially an inflammation of the trachea and larger bronchi.

2.—AETIOLOGY

ⁿ The cause of whooping-cough is a small Gram-negative bacillus, *Haemophilus pertussis* (bacillus of Bordet and Gengou), the responsibility of which for the disease has been established on the following grounds: (i) the organism can be recovered from patients with whooping-cough but is not found in healthy persons; (ii) the blood of those who have had whooping-cough contains bodies which agglutinate *H. pertussis* and give a complement-fixation reaction to it; and (iii) applica-

tion of the living organism to the nasopharynx of a susceptible person produces an attack of whooping-cough.

Both sexes are equally susceptible and the infection can occur at any age. Its greatest incidence is in childhood, probably because most adults have acquired immunity either as a result of attack or through repeated minor infections. Young babies are liable to infection and the apparent rarity of the disease in early infancy is due to the fact that the symptoms are not usually typical at that age. An attack of whooping-cough conveys an immunity which, without being complete, is sufficient to ensure that second attacks are rare. *Incidence* *Immunity*

The incubation period varies from one to three weeks. When another disease, such as pneumonia, is present at the same time the earlier symptoms may be masked and develop only after improvement in the concurrent illness. Such a prolongation of the time of incubation is apparent and not real. Although the period of infectivity is different for each patient, it is a safe rule to consider a patient infective for six weeks from the time of the first whoop. After that he may safely mix with susceptible children, even though his paroxysms continue. If facilities for bacteriological examination are available it may be possible to prove the absence of *H. pertussis* before the six weeks have elapsed and to curtail the period of isolation (see also p. 619). *Incubation period* *Period of infectivity*

3.—BACTERIOLOGY AND MORBID ANATOMY

Physical examination may help little in establishing a diagnosis but laboratory investigation brings considerable aid in doubtful cases. By suitable methods the bacillus causing the disease may be recovered in the earlier stages and this provides the most conclusive test. *H. pertussis* grows on a potato-lactic-acid-blood-agar medium. If this is put up in Petri dishes and exposed to an infected patient during a bout of coughing, colonies of the organism can be grown. The use of 'cough-plates' may become a routine method of diagnosis and of determining the period of infectiveness in individual cases. The test is widely used abroad; in this country Smith demonstrated its utility in a boys' school both for recognition of early or mild cases and for making possible a speedy return to school of those whose period of infectivity is short. *Cultivation of organism* *'Cough-plates'*

In the catarrhal and early spasmodic stages of whooping-cough there is an alteration in the white blood count. The total number of white cells is increased, the increase being made up almost entirely of lymphocytes which may number 15,000 to 30,000 per c.mm. Such a blood count in conjunction with a suggestive cough gives reasonable grounds for a diagnosis of whooping-cough. *Blood count* *Lymphocytosis*

As the disease progresses, the patient's blood acquires complement-fixation substances, agglutinins and precipitins against *H. pertussis*. Because they do not reach their full amount until the fourth to the *Complement-fixation substances*

sixth week of the disease, tests for their presence can hardly be utilized as a diagnostic measure, though such tests have their use in assessing the success of prophylactic treatment with vaccines or in determining whether any individual has a natural immunity to whooping-cough. The same objection can be made to the cutaneous reaction to small doses of *H. pertussis* which is observed only in the later stages of the disease and for some months afterwards. The erythrocyte sedimentation-rate increases in whooping-cough, though not in proportion to the severity of the disease. This relatively small increase in the sedimentation-rate may sometimes be of service in confirming a diagnosis.

The anatomical changes produced by whooping-cough as opposed to its complications are not as a rule striking. The body of a child dead of uncomplicated whooping-cough shows some reddening of the trachea and larger bronchi. If death has taken place early in the illness, suitably-stained sections of the trachea show *Haemophilus pertussis* lying closely packed under the lining membrane. Later in the illness the lungs are studded with recently-formed emphysematous bullae. The rupture of such a bulla into the mediastinal fold of the pleura on occasions gives rise to gross surgical emphysema extending up under the skin of the neck and face. Such an occurrence, though by no means always fatal, leads to post-mortem manifestations as typical as those it gives rise to in life. Less frequently an emphysematous bulla bursts into the pleural cavity leading to pneumothorax with collapse of the affected lung. In fatal cases in young children and babies, multiple small haemorrhages are sometimes found scattered over the meninges and in the substance of the brain and spinal cord.

4.—CLINICAL PICTURE

An attack of whooping-cough starts insidiously. Symptoms in the first days are not unlike those of a cold in the head. The catarrhal stage lasts from three to ten days, towards the end of which time cough, rather than running from the nose, begins to dominate the picture. Physical examination reveals, at most, reddening of the throat and occasional coarse râles over both lungs.

The occurrence of a typical cough marks the transition from the catarrhal to the spasmodic stage. The paroxysm has easily recognized features. Often it is brought on by some act such as that of swallowing, crying, or gagging. The patient gives a series of short sharp coughs during the course of a single expiration. The series lasts longer than would seem possible in one breath and towards its end the patient shows signs of distress. His colour, first red, changes to blue; the eyes water, become injected, and start out from the head. The tongue projects and saliva dribbles from the mouth. The veins of the neck are distended. When at last the cough stops, the patient draws in his breath with a typical whoop. The process is usually repeated twice

or thrice. A plug of mucus is sometimes brought up at the end of the attack. The stress of the paroxysm usually leads to emptying of the stomach, especially if it takes place during or soon after a meal. An immediate effect of an attack may be a convulsion or a transitory loss of appreciation of place and time. Always after a severe bout of coughing the patient sinks back pale and exhausted. It is surprising how quickly this phase passes and the child resumes his interrupted occupation.

*Vomiting**Convulsion*

There is considerable variation both in the frequency of the bouts of coughing and the period over which they persist. In a severe case they may occur as often as once every half-hour, though it is uncommon to hear more than twenty-four in as many hours. The more fortunate patients escape with a quarter that number, even at the height of the disease. The duration of liability to bouts of coughing varies from a few days to several months. An average duration is from four to six weeks. The weather has some influence on the length of the illness, for whooping-cough in the winter is liable to last longer than an attack of the same severity contracted in the summer, probably because of the prevalence of other respiratory infections in the colder months.

*Incidence of paroxysms**Influence of weather*

Other respiratory infections lead not only to the prolongation but also to the recurrence of the symptoms of whooping-cough. Thus a child who has recovered from whooping-cough and develops pneumonia six months later sometimes starts to whoop again. Such a patient is not infective during the relapse. This is a point of considerable importance in the management of a children's ward. Isolation is not necessary for a patient who whoops if it is known, without any doubt, that he has recovered from an attack of whooping-cough within the previous twelve months.

Influence of other infections of cough

The symptoms of whooping-cough are not always so characteristic as those just described. Up to the age of a year babies rarely whoop, though the paroxysm of coughing is otherwise the same as in older children. Vomiting is perhaps more prominent in infancy than in the older patients. The cough, even without the whoop, can be easily recognized and, as long as it is understood that absence of the whoop does not affect the diagnosis, difficulty does not arise on this score. More confusing are those cases in which the cough is suppressed by some severe concurrent illness. Only too often a patient, convalescent from pneumonia or acute otitis media, starts to whoop and events prove that he was infective long before the diagnosis of pertussis could be made. Besides these simple variations in the symptoms, cases have been reported in which paroxysms of sneezing have taken the place of the more usual cough (Moncrieff and Lightwood). Very young babies may have a form of the disease resembling encephalitis more than a respiratory infection.

*Symptoms in infants**Sneezing*

The scanty physical signs, the scarcity of which in the catarrhal stage is mentioned on page 618, are hardly more helpful in the paroxysmal stage in establishing a diagnosis. Early in the illness there is fever, though the temperature rarely exceeds 100° F. In infancy there is a marked rise in the

*Physical signs**Fever and respiratory rate*

respiratory rate at the onset. The conjunction of a low fever with a disproportionately high respiratory rate sometimes suggests the diagnosis before the occurrence of the cough. As the disease develops, the patients have pale puffy faces, an appearance which may be compared to that seen in parenchymatous nephritis or in leukaemia. If the attacks are frequent and the lower incisor teeth have been cut, an ulcer can often be seen on the under surface of the tongue in front of the frenum. Examination of the lungs, even at the height of the illness, reveals very little. There are occasional metallic râles best heard over the back. In some cases there is evidence of enlargement of the mediastinal glands shown by impairment of percussion note between the scapulae and an extension downwards beside the upper dorsal spines of the area over which whispering pectoriloquy can be heard. Bronchitis or pneumonia complicating whooping-cough add their own manifestations to the physical findings. Towards the end of the illness, except when the attack has been very mild, a greater or less degree of emphysema of the lungs develops and can be detected for weeks or months afterwards. Similarly dilatation of the venules in the skin of the cheeks and over the back of the chest is common in the later stages of the disease and this, too, persists for some months. Occasionally there occur in whooping-cough haemorrhages from the rupture of small blood-vessels in the conjunctivae or even in the skin of the face.

*Ulcer on
frenum*

Haemorrhages

5.—COMPLICATIONS AND SEQUELAE

Complications

Bronchitis

The commonest complication of whooping-cough is bronchitis. This is understandable in view of the nature of the disease and the opportunity, especially during the winter months, to acquire a superadded infection. Bronchitis may prolong the symptoms but except in infancy and in old age it hardly adds to the risk of the illness.

Pneumonia

Secondary pneumonia is a more serious complication. The infection spreads out from the bronchi and bronchioles to the adjacent alveoli in the manner described by McNeil, Macgregor, and Alexander. The resolution of the pneumonia is not immediate but by a process of fibrosis, leading to prolonged illness. Secondary pneumonia is one of the fatal complications of whooping-cough.

*Effect on
pulmonary
tuberculosis*

Hardly less serious is the effect of whooping-cough on an underlying tuberculous infection. By the age of five many town-dwelling children have had a tuberculous infection of their lungs. In normal circumstances the result of the infection is seen only as a primary (Ghon) focus and a greater or less involvement of the glands of the root of the lung and mediastinum. Whooping-cough allows such latent infection to become active. The morbid process in the affected gland lights up and tends to spread into the surrounding tissues. Hence a massive tuberculous involvement of the lung or a generalized spread

of tuberculosis from a previously dormant infection must be regarded as a direct complication of whooping-cough.

Convulsions may be a concomitant of the disease but more serious disorders of the nervous system are sometimes seen. Haemorrhages into the brain, especially during early infancy, may complicate the picture. More confusing is the coma seen in young babies. Physical examination suggests inflammation of the brain but after death the findings are at most multiple small haemorrhages round the vital parts of the brain-stem. *Complications in nervous system*

Disturbance of digestion is typical of the disease. In the very young vomiting and diarrhoea exceed the degree expected from the cough. The condition is one of secondary gastro-enteritis which on its own account may prove fatal. *Digestive disturbance*

Sequelae

The sequelae follow from the complications. Secondary pneumonia may lead to fibrosis of the lungs, empyema, or bronchiectasis, and the latter in its turn to a cerebral abscess. Damage to the central nervous system by haemorrhage, if not fatal, may be perpetuated as a spastic paralysis. Exacerbation of tuberculosis of the lungs or mediastinal glands may give rise to invalidism long after the whooping-cough has disappeared.

6.—PROGNOSIS

The risk to life from an uncomplicated attack of whooping-cough in a healthy child more than a year old and in good surroundings is slight. Under that age and in old age the disease is often fatal. The danger of the disease in childhood is rather through its complications, such as pneumonia and tuberculosis. For the same reason, later health may be impaired. The chance of disability from chronic pulmonary disorder, both tuberculous and non-tuberculous, makes whooping-cough one of the most dangerous of the preventable diseases.

7.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Typical whooping-cough can hardly be confused with any other illness. Diagnosis is made either by hearing the cough or by recovering the causal organism. In the minority of cases suspicion aroused by a cough is confirmed by one or other of the clinical or laboratory investigations outlined above. Difficulty in correct diagnosis, however, does arise in the less characteristic cases.

The pallor, especially when associated with a high lymphocyte count, may suggest a diagnosis of lymphatic leukaemia. Absence of splenomegaly and of adenitis helps to distinguish whooping-cough. Mediastinal glands enlarged by tuberculosis or Hodgkin's disease and pressing on the trachea sometimes cause a paroxysmal cough very like whooping-cough, but not having an actual whoop. A radio- *Diagnosis from lymphatic leukaemia and enlarged mediastinal glands*

graph of the chest which shows the presence of the enlarged glands will help to distinguish whooping-cough from the other two diseases. A differential blood count will often show an eosinophilia in Hodgkin's disease or an altered lymphocyte-monocyte ratio in tuberculosis; these features are lacking if the disease is whooping-cough, which has itself a characteristic blood picture already mentioned. In whooping-cough the erythrocyte sedimentation rate is increased but little; in tuberculosis, and still more in Hodgkin's disease, the rate tends to be very high.

Diagnosis in infants

In young babies difficulty is encountered if the symptoms are wholly cerebral or wholly alimentary. In the former event examination of the cerebrospinal fluid helps to exclude other disorders, though if the fluid is blood-stained doubt may remain for a time. Gastro-enteritis arising from whooping-cough may be identified if a culture of the *H. pertussis* is obtained, but often it is the course of the illness rather than any specific test which discloses the underlying cause.

8.—TREATMENT

Preventive

Isolation

Isolation of patients with whooping-cough does not effectively stop the spread of the disease for patients are infective in the early catarrhal stage and in many the attack is so mild that it cannot be recognized.

Prophylactic vaccines

Prophylaxis by means of vaccines has in the past given uncertain results but more information is now available about the type of bacterium to be used, the doses to be given, and the time that must elapse before protection is present. The vaccine must be made from a recently recovered strain of *H. pertussis* which has been cultured on a medium containing blood (phase I organism). If large doses are to be used the blood in the medium should be human to prevent reactions. Two types of vaccine are in use. The first is an emulsion of the bacteria killed by heat, the second the products obtained from grinding up live bacteria. The tendency is to give as large doses as can be tolerated without a local or general reaction. Sauer recommended twenty or thirty thousand million bacteria given at weekly intervals for three weeks. Others have obtained satisfactory protection with rather smaller doses. After such treatment antibodies take from two to six weeks to appear in the blood. The vaccine must therefore be given at least that time before exposure if the patient is to be protected. Even when these conditions are fulfilled the protection is not always complete, but if an attack of whooping-cough does occur later it tends to be short and mild.

Convalescent serum

The results obtained from attempts to give contacts a passive immunity by the injection of convalescent serum have been disappointing and in its present form this method is useless. I have found very small doses of vaccine have offered the best method of protecting contacts. Three million bacteria followed two days later by five million are given starting as soon after exposure as possible. On nine occasions susceptible

patients in a children's ward have been treated in this way after the discovery of a case of whooping-cough in the ward. In eight instances there were no secondary cases and in the ninth one child only developed the disease.

Symptomatic

There is no specific treatment of whooping-cough. Vaccines and convalescent serum have no beneficial effect once the disease has developed.

The patients are more comfortable in the open air; they have fewer paroxysms and those they have are shorter. They should be nursed out of doors in bed during the febrile stage and should be allowed up to play outside as soon as the fever has gone. In Great Britain it is usually impracticable for children to sleep out of doors, but much can be done for them at night by having windows wide open. Clothing should be arranged so that the patients do not feel cold. *Environment*

Hot food and coarse residue-containing food tend to bring on attacks of coughing and should be avoided. Some children, though not all, tolerate their meals best if these are really cold. In such cases ice cream, iced stewed fruits, and junkets should be used to vary the diet. In every case during the height of the paroxysms milk and eggs in various forms must form the basis of the diet. Infants must be given enough fluid and for a week or two the caloric value of their diet may be neglected. If diarrhoea and vomiting are present the diet must be modified to control these symptoms. In all patients a liberal allowance of food must be made to compensate for that part which is vomited. *Diet*

In the catarrhal stage of whooping-cough belladonna gives some relief and the patient should be given full doses for his age. In the paroxysmal stage an attempt must be made to depress the cough reflex. A linetus of syrup of tolu and oxymel of squill containing in each dose from 3 to 20 minims of camphorated tincture of opium according to age is sufficient in mild cases. In babyhood chloral hydrate 3 grains in syrup can be used to promote sleep. In older patients phenobarbitone in doses of $\frac{1}{2}$ grain once to three times a day often reduces the number of paroxysms. Ether in olive oil given per rectum has been used to diminish the number of paroxysms. Often its effect is disappointing, though occasionally it works well. It is a treatment best reserved for young patients in whom exhaustion is becoming extreme. The very multiplicity of other remedies for whooping-cough is evidence that none is wholly effective in alleviating the distressing symptoms. *Drugs*
For cough

Besides treatment directed towards the symptoms the patients should be given help in warding off complications. Diet and fresh air can be reinforced with large doses of vitamins A and B. The natural forms of vitamin A in fish-liver oil may be nauseating and it is best offered in a tasteless concentrate. Finally, after the infective period is over, the patient should be sent for a holiday to encourage complete healing of the inflamed pulmonary and mediastinal lymph glands. *Prevention of complications*
Vitamins

Evidence is accumulating that by giving sulphanilamide or its

*Sulph-
anilamide*

derivatives the complications of whooping-cough can be minimized. Sulphanilamide has not been shown to cut short the illness itself. There is undoubtedly scope for this group of drugs in treating the secondary effects of whooping-cough. Caution must be observed in their application. Sulphanilamide is a potent drug but it has some disadvantages. It is possible that its later ill-effects on kidneys and gonads are not yet fully known, and that until they are its wholesale application to prevent complications of whooping-cough cannot be recommended.

Although the treatment of the disease is largely palliative, much can be done both to prevent severe attacks of whooping-cough and to avoid disastrous after-effects and there is room for wider application of these principles.

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WILSON'S DISEASE

See DERMATITIS, EXFOLIATIVE, Vol. III, p. 619; and
 HEPATO-LENTICULAR DEGENERATION, Vol. VI, p. 443

WOOLSORTERS' DISEASE

See ANTHRAX, Vol. I, p. 629

WRITERS' CRAMP

See CRAMP, Vol. III, p. 455

WRY-NECK

See TORTICOLLIS, p. 48

XANTHOMA AND XANTHELASMA

See SKIN DISEASES: TUMOURS, Vol. XI, p. 257

XANTHOMATOSIS

See LIPOIDOSIS, Vol. VIII, p. 68

XERODERMA PIGMENTOSA

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Reference may also be made to the following title:

BRONZING OF THE SKIN

1.—DEFINITION

(*Synonyms*.—Xeroderma pigmentosum; dermatosis Kaposi; lentigo maligna; atrophoderma pigmentosum)

1614.] Xerodermia pigmentosa is a rare congenital disease showing both atrophic and hypertrophic changes in the skin, particularly in the areas exposed to sunlight. Malignancy ultimately supervenes.

2.—AETIOLOGY AND MORBID ANATOMY

Incidence This disease, originally recognized by Kaposi, is a great rarity, particularly in Great Britain. The first signs generally become evident before the victim has reached the age of 2 years. Later onset is very unusual, indeed the great majority of the affected children are attacked during early infancy. The malady shows definitely familial features. The incidence in the two sexes is equal but it is usual for only one sex to be affected in one family. In spite of this well marked congenital factor the disease is not hereditary. Parental consanguinity is present in 11·8 per cent of cases. Associated paralyses and paroxysmal haemoglobinuria have been described.

Pathogenesis For years clinical experience indicated that sunlight played a part in

the causation of this disease and recent work has provided even more exact knowledge. Rothman proved that no sensitizing substances can be extracted from the urine and that no sensitivity can be transferred to animals by the injection of a patient's blood. Thus it would seem that the malady is not due to a metabolic disorder such as is seen in hydroa aestivale. The same author discovered that exposure of the unaffected skin of one case to ultra-violet rays gave rise to a long-standing erythematous reaction and ultimately to telangiectases and warts; visible light rays, heat rays, and X-rays did not cause any changes. In Lynch's case there was not any sensitivity to radiations of wave lengths longer than 310 millimicrons (0.310μ). As few radiations shorter than 297 millimicrons (0.297μ) reach the earth's surface it would seem that the important sensitizing range lies between these figures (for wave lengths of the various parts of the solar spectrum see Vol. I, p. 182, and Vol. VI, p. 386). The same wave lengths, however, may not be responsible for the changes in all cases, as Bertaccini obtained a reaction by exposure to soft X-rays. The mode of action of the rays is not known, but it seems that they act physically upon congenitally abnormal cells.

Whether or not there is an underlying defective innervation is unknown; it is, however, unlikely because the distribution of the eruption always corresponds to the areas of exposure both in this disease and in the very similar biotripsis.

The histological picture shows a thickened horny layer over a thick hyalinized layer of epithelial cells, fusion of which often renders them completely indistinguishable. The Malpighian and germinal cell layers are highly atrophic. In the early stages there is a small-celled infiltration in the papillary layer and round the adnexa. Later the follicles and sweat-glands atrophy. Pigment is present in most parts of the skin including the corium and particularly in the basal layer. The white fibrous-tissue is also atrophied but the amount of elastic fibres is increased; the most common vessels seen are dilated venules. Ulcerations, pyogenic infections, warts, and carcinomas are all typical sequelae though mixed basal- and squamous-celled growths are sometimes seen. Pure basal-celled tumours occur occasionally and melanotic carcinomatous deposits have been found in the liver at necropsy.

Morbid anatomy

3.—CLINICAL PICTURE

In a typical case six different lesions cover the exposed areas of the body, i.e. the whole of the face and neck and the immediately adjacent upper parts of the chest and back, the lower thirds of the arms and the whole of the forearms, being rather less marked on their inner surfaces, and also on the dorsal aspects of the hands and fingers. The distribution over the legs and feet corresponds to that over the upper limbs, but the thighs are only occasionally involved.

Distribution of lesions

- Pigmented patches* The first signs often consist of erythema and oedema after the child has been exposed to sunlight. In many patients this stage is either absent or so transient as to escape notice and in them the first sign consists of freckle-like pigmentation thickly covering the exposed skin. The individual patches vary in size from that of a pin's head to that of a bean and their tints range between a pale yellowish-fawn and a deep sepia. This discoloration persists, increasing in density until the third or fourth year of life. About this time it is noticed that the skin is thin, dry, and rough, bearing the minute exfoliative flakes generally associated with dryness. There are, however, no signs of true ichthyotic xerodermia.
- Atrophic spots* Small white spots of atrophy now become evident among the patches of pigment. They occur in relatively small numbers but tend to be more numerous and to coalesce on the cheeks immediately below the eyes. Here larger areas of white shining scars gleam against the brown background. These atrophic disks have sometimes been noticed before either erythema or pigmentation has occurred, but they are generally detected at this stage of the disease.
- Eye symptoms* By this time hyperaemia of the conjunctivae, blepharospasm, and photophobia attract attention to the eyes. Ulceration is not uncommon, together with haziness of the cornea.
- Telangiectases* During the next few months striate and stellate telangiectases develop not only interspersed with the pigmented patches but also sometimes on the white areas where their colour stands out sharply. The punctate dilated vessels may form tiny convex domes on the skin.
- Ulceration* When the atrophic changes in the epidermis have rendered it thin, ulceration results from direct trauma and also from irritation or direct pus inoculation from the ocular discharges. The ulcers are chronic, superficial, and covered by yellowish or greenish crusts. After they have healed the scars may contract and produce ectropion and considerable disfigurement.
- Warts* By the time the patient is 8 years old many small warts have appeared which in their general features resemble early senile warts and are scattered irregularly over the affected surfaces, always arising on the 'freckles'.
- Carcinomatous changes* Carcinomatous changes now rapidly supervene, the growths developing directly from warts or ulcers, particularly round the eyes and mouth. The masses are usually red and fungating but may be ulcerative. Very rarely one or two of such squamous-celled growths resolve, steady progression being the rule. The glands become affected with the result that death generally occurs before the age of twelve.
- Atypical cases* Such is the inevitable sequence of events in the great majority of cases, but a few individuals have survived for many years with occasional intermissions of quiescence. Rare mild cases occur in which the signs are almost limited to the 'freckles'.
- Relation to other conditions* In a very few recorded examples the disease started suddenly late in life and these patients may form a connecting link between this malady

and the condition so commonly seen in the skins of those who have been much exposed to sun and weather. In such individuals atrophic spots, pigmented patches, telangiectases, warts, and even squamous-celled carcinomas are seen on exposed surfaces and in particular on the backs of the hands. This is the condition to which Cheattle gave the name 'biotripsis' or 'life wear' (see also Vol. III, p. 611, and Vol. XI, pp. 205 and 233) and it is identical with the 'seaman's skin' of Unna. In xerodermia pigmentosa the same five changes are present and, in addition, ulceration.

4.—TREATMENT

Treatment may be divided into two distinct parts. If the patient is seen before serious damage has occurred, protection of the skin and eyes is essential. To this end darkened rooms and various coloured veils have been used. Tinted glasses must be worn and the skin may be covered with a paste containing burnt umber or 10 per cent of quinine sulphate in a basis of soft paraffin, or 10 per cent tannic acid. The patient should not be allowed out of the house in bright sunlight and even at other times should shade the face by an umbrella. *Protection of skin and eyes*

Later the simpler eye changes and ulcerations may be treated by ordinary antiseptic methods, but these must be carried out rigorously. Thus diligent bathing of the eyes with boric acid lotion and the dressing of ulcers by carbolyzed lotions are indicated. *Local applications*

Warts and early epitheliomas of both types must be dealt with thoroughly as soon as they appear. They may be excised, but they also respond well to exposure to radium or X-rays. Larger growths must be removed surgically and ulceration into the chamber of the eye demands enucleation. Much relief can be afforded by these measures although the ultimate outlook in typical cases is still hopeless. *Treatment of growths*

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XEROPHTHALMIA

See BLINDNESS, Vol. II, p. 451; DIETETIC DEFICIENCY DISEASES, Vol. IV, p. 57; and VITAMINS, p. 594

YANGTSE VALLEY FEVER

See BILHARZIASIS, Vol. II, p. 331

YAWS

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1.—NOMENCLATURE AND DEFINITION

1615.] Among English-speaking peoples the term yaws, adapted from a *Synonyms* native word in the West Indies (Labat, 1694), is in general use. Framboesia (Sauvage, 1750), derived from the French word *framboise* (a raspberry), on account of the raspberry-like appearance of the typical skin lesions, is also commonly employed by French, German, and British writers, though the name more often found in French literature is *pian*. In South America and other countries where Spanish or Portuguese is spoken the designation bubas or bouba is more common though the expression appears to include affections other than yaws. A multitude of other names exist in local use in different parts of the world, of which the best known are: parangi (Ceylon), buena (Burma), puru (Malay), patek (Dutch East Indies), koko (Fiji), gattoo (West Africa),

and dubi (Gold Coast). Some American writers who profess to be unable to distinguish yaws from syphilis speak of treponematoses to include both diseases.

Definition

Yaws is a specific contagious disease, wide-spread among the native populations of warm countries, caused by *Treponema pertenue* (Castellani, 1905), characterized by an initial inoculatory lesion followed by the appearance, in successive crops, of a granulomatous skin eruption peculiar to the affection and associated with bone pain and other general symptoms, and sooner or later, in a proportion of cases, by gummatous-like lesions of the skin and bone.

Earliest recognition

The date of the first recognition of yaws, as in the case of many other diseases, is uncertain; probably it was distinguished as a clinical entity in the latter part of the 15th century. As a cause of invalidity and permanent disability its economic importance has been recognized since the beginning of the slave trade between West Africa and America. In June 1905 Aldo Castellani described *Treponema pertenue* as the causal organism.

Causal organism

2.—AETIOLOGY

(1)—Geographical Distribution

Tropical distribution

Framboesia has always been considered to be essentially a tropical disease, that is to say a disease restricted to the belt lying between the tropics of Cancer and Capricorn. This is very nearly true and truer still if the tropics were defined by the isotherms delimiting a tropical climate together with heavy precipitation. Though an occasional 'imported' case may appear at the southern coastal ports of North America and even in Europe, the disease is nowhere there endemic.

North and South Africa

In northern Africa yaws does not occur, Morocco, Algeria, Tunisia, Egypt, and the northern Sudan being exempt. The single case recorded from near Algiers in 1901 as belonging 'to the confused group of conditions called framboesiform' was almost certainly not a case of yaws. A dozen cases said to be yaws were reported in 1915 from Tripoli. South Africa is similarly exempt from endemic yaws. The exceptional outbreak among Johannesburg miners has a peculiar significance and is referred to below (see p. 643). Cases have also been reported from Kimberley.

Tropical Africa

Below is given a list of countries belonging to tropical Africa with some figures to indicate the incidence of the disease. Sudan, prevalent; Rio de Oro, no records; Senegal, only found in parts of Senegal and then in small numbers; Gambia, not uncommon—in 1933, 403 cases treated; Portuguese Guinea, no records; French Guinea, 21,982 cases treated in 1933 and 42,032 in 1934; Sierra Leone, 16,929 cases of yaws in 1929: 14,082 in 1930: 7,449 in 1931: 5,891 in 1932; it was estimated that 24.7 per cent of the population of the Northern Province and 54.0 per cent of the Southern and Central Provinces were infected; Liberia, in the hinterland, 80 per cent of the children are infected and 30 per cent of the adults exhibit 'crab yaws'; Ivory Coast, very wide-spread in the forest

hinterland: 50,696 cases treated in 1933 and 68,581 in 1934; Gold Coast, in 1932-3, 34,544 males and 27,653 females treated; Togo, very prevalent: 25,982 cases treated in 1933 and 31,346 in 1934; Dahomey, 26,151 cases treated in 1933 and 25,738 in 1934; French Nigeria and Sudan, comparatively rarely recorded; Nigeria, 80,136 cases treated in 1932; Cameroon, 33,754 cases treated in 1933 and 42,064 in 1934; French Equatorial Africa, prevalent in Gabon, in Ouessou and Nola, Moyen Congo and Tchad and Oubanghi Chari, where, in 1933, 20,000 cases were treated; Belgian Congo, 43,773 cases of yaws treated in 1932; Somaliland, a few cases have been reported; Italian Somaliland, reported as wide-spread in 1928; Ruanda-Irundi, very prevalent: 103,711 cases recorded in 1930: 92,050 in 1931: 80,126 in 1932; Uganda, in 1932, 43,773 cases of yaws treated; Kenya, 70,253 cases treated in 1927: 86,617 in 1928: 89,615 in 1929; Zanzibar, 4,659 cases treated in 1931: 4,432 in 1932: 5,935 in 1933; Tanganyika, 74,638 cases treated in 1925: 96,624 in 1926: 120,263 in 1927: 127,439 in 1928: 126,328 in 1929: 137,112 in 1930: 112,128 in 1931: 114,115 in 1932; Portuguese East Africa, present--no figures available; Nyasaland, 1,707 cases treated in 1930: 2,524 in 1931: 2,672 in 1932: 1,966 in 1933; Northern Rhodesia, one-quarter of the total population of 53,000 estimated in 1926 to have yaws: 2,279 had been treated; Southern Rhodesia, yaws not reported; Angola, present, but no figures available; Bechuanaland, a few cases observed: 86 in 1933; Madagascar and Comoro Islands, yaws endemic: 10,203 cases in 1934; Mauritius: it is stated that yaws does not occur; Seychelles, none.

In northern and central Asia and Japan the disease is unknown. In *Asia India* India there are scattered endemic areas in Bengal, Orissa, Central Provinces, and Haiderabad, but no figures are available. It is probable that, when search has been made among many of the more primitive forest tribes of India, yaws will be discovered to be much more widely spread than is at present supposed.

In Ceylon, Malaya, French China, the East Indies, and the Pacific Islands the disease is wide-spread.

Ceylon, 24,841 cases treated in 1929: 23,684 in 1930: 24,708 in 1931: 23,208 in 1932: 18,368 in 1933; Burma, yaws endemic, no figures available; Assam, yaws endemic, no figures available; Siam, yaws endemic; Malaya, yaws widely spread: in Kelantan, 7,509 cases treated in 1928: 8,288 in 1929: 16,581 in 1930: 21,004 in 1931: 26,468 in 1932; in Trengganu, 3,390 in 1929: 3,386 in 1930: 2,601 in 1931: 2,686 in 1932; in Johore, 4,977 in 1931: 4,566 in 1932.

French China: the disease is widely distributed in Annam, Tonkin, Cochin China, Saigon, Laos, Cambodge, and Cambodia. It is an inevitable disease of childhood in all the forest zones. Dutch East Indies: with an estimated population of 45 millions some 890,000 cases of yaws were treated between 1919 and 1934. In Sumatra the incidence varies between 12 and 90 per cent. The same is true of Java where in 1924 1,600,000 injections were given in the treatment of the disease. In

Celebes, 22,789 injections were given in 1928. Timor is heavily infected and in Sumba 70 per cent of the inhabitants suffer from framboesia. Borneo: it is stated that in the central region of Papua yaws is very prevalent and that every Dyak child in Southern Borneo is infected with the disease. It occurs also in Sarawak. Formosa: the disease has been reported from the southern part of the island. Philippine Islands: in some areas 70 per cent of the population is attacked; 31,040 cases were treated in 1923-4. Caroline and Marianne Islands (including Guam): yaws is prevalent. French Pacific Islands: yaws is wide-spread in the Loyalty Islands, in Wallis, Futuna, New Hebrides, and New Caledonia. British Solomon Islands: 21,628 injections were given in 1932 and 11,998 in 1933 in the treatment of yaws cases. Fiji: it is believed that 100 per cent of the native population is infected with yaws, mostly contracted in childhood. Gilbert and Ellice Islands: in 1932, 5,536 injections given for yaws; Samoa: 88.9 per cent of the total population examined; 67.7 per cent of these gave a history and 60.6 per cent showed evidence of yaws infection; 74,088 injections given in 1932 and 38,644 in 1933. In many other groups of islands the disease is wide-spread but no figures are available.

Australia

In Australia yaws is endemic in the northern half of the continent, chiefly in the Northern Territories, but it has been argued on the discovery of bones showing lesions ascribed to yaws that the disease was distributed all over Australia a century ago.

Central America

Although yaws is prevalent in the East Indies, central American countries appear to be spared. The disease is not reported from Mexico, Yucatan, Honduras, British Honduras, or Salvador. On the other hand it is said to occur in Nicaragua and Guatemala, and a few cases have been reported from Panama. In Costa Rica the disease was first noticed in 1924, 6 to 16 per cent of the population being said to be infected. The disease is unknown in the Bahamas and, although it existed at one time in Bermuda, it has now disappeared. Cuba: the disease is present but no statistics are available. Jamaica: yaws is extremely prevalent in some rural populations. The following figures have been extracted from the reports of the Jamaica Yaws Commission:

Jamaica

Table to show Incidence of Yaws in Jamaica

YEAR	AREAS SURVEYED	TOTAL POPULA- TION	NO. OF CASES TREATED	TOTAL NO. OF TREAT- MENTS	NO. OF WASSERMANN AND FLOCCULATION TESTS
1932	590	2,728	16,000
1933	5	12,605	2,616	10,541	26,444
1934	7	22,578	4,844	21,856	26,767
1935	8	35,323	8,337	45,755	15,162
1936	8	38,487	7,923	45,721	25,671
Total	- 28	108,993	24,310	126,601	110,044

Haiti: 80 per cent of the population in some areas affected—in one district in one year (1925-6) 167,267 cases treated; Porto Rico: there is said to be a single focus of yaws; Virgin Islands, Antigua, Guadeloupe, Monserrat, Martinique: yaws present, but the disease is said to be diminishing in numbers in the French islands; St. Lucia: 1,422 cases treated in 1932; St. Vincent: 6,091 cases treated in 1932; Grenada: 1,500 cases treated in 1932; Dominica: 2,400 cases treated in 1932. The figures for most of the other islands are similar. In Trinidad the disease is also common.

Information regarding the distribution of yaws in South America is very scanty; it is believed to be endemic in Venezuela; in Colombia it is wide-spread in the coastal and riverine zones. In British and French Guiana the disease was once common but is now rare, though in Dutch Guiana it is prevalent. Yaws has been reported from Peru, and is wide-spread in certain provinces of Brazil, in Bahia, and also in Parahyba, where 30,000 cases were found in a population of 1,200,000. More recently the disease has been discovered in Minas Geraes. Information as regards Ecuador, Bolivia, and Paraguay is not forthcoming. The disease has not been reported from Argentine or Chile.

In 1694 an outbreak of what was called 'sibbens' or 'sivvens' (*sivvi*—raspberry, Celtic) occurred in Scotland. This and the 'button-scurvy' in Ireland later have been by some writers considered akin to yaws, and some would identify sivvens with framboesia. There can, however, be little doubt that these were outbreaks of epidemic syphilis exactly comparable to others which occurred in Europe and elsewhere during the same epoch. The clinical manifestations described resemble those of the endemic syphilis among the Bedouin Arabs of the Euphrates Valley described by Ellis H. Hudson.

Framboesia tropica, as the name implies, and as has been shown in dealing with the geographical distribution, is practically limited to warmer countries. The precise significance of this association remains uncertain. The evidence suggests that a number of factors commonly obtaining in the tropics have a bearing on the chance of contagion rather than that a hot climate plays any more specific part. In the warm belts the more primitive peoples are found, living under primitive conditions in regard to clothing, housing, and food, the adults wearing little bodily covering and the children as a rule none; all are exposed to multiple minor skin injuries. Personal cleanliness may be of a low standard and personal contact is close owing to their methods of living; their general resistance to disease is low owing to multiple infestations with protozoal and helminthic parasites and subsistence on a deficient diet. At the same time a warm and moist climate conduces to the propagation of flies which may play an important part in transmitting the disease.

It was at one time believed that yaws did not occur above a very moderate altitude, but the disease has since been found in Sumatra above 3,000 feet, in the Philippines at over 6,000 feet, in Formosa at 5,000 feet, and in Africa at more than 5,000 feet.

*South
America*

*Early
reported
outbreaks in
Scotland and
Ireland*

*Climatic
factors
influencing
distribution
of disease*

Altitude

Rainfall probably plays an important part, as recently shown in Jamaica, where the incidence is much higher in areas of greater rainfall and where it has been shown that recrudescence of active lesions is much commoner in the wet season than in the dry season. There is a positive correlation between the incidence of yaws in Jamaica and rainfall, but whether this association is direct or indirect the Yaws Commission could not decide. Greater precipitation means more luxuriant vegetation, greater liability to trauma, and possibly an increase in the number of flies which might act as vectors. In barren arid regions of the tropics the disease does not seem to occur.

(2)—Sex and Age Incidence

The sexes are equally susceptible. When there is an inequality in the chances of infection owing to the sexes living under different conditions, there may be a difference in the sex incidence of the disease. This is shown by figures from Jamaica, where the predominance of males over females is most marked from infancy to adolescence but disappears in later adult life. Elsewhere the number of female adults who contract the disease may be nearly double that of the males, a fact explained by the observation that women often gain their infection from children.

Trans-placental transmission of yaws does not occur and hereditary yaws comparable to congenital syphilis is unknown. A woman never gives birth to a child suffering from the disease; the two or three recorded cases in which 'congenital yaws' has been suggested do not bear criticism. Infection of the infant may take place at birth and a primary lesion at the umbilicus can occur.

It has been suggested that, since yaws is commonly contracted in childhood, as is mentioned below, the power of trans-placental transmission to the foetus has been lost when the child-bearing age is reached; this is an interesting speculation, but the fact that no case of transmission to the foetus by a mother suffering from active yaws during the pregnancy has ever been recorded weighs against this view.

Age incidence has sometimes been considered as if the young were more susceptible than adults. It may, however, be pointed out that all ages appear to be equally susceptible. The early age at which infection commonly occurs in endemic areas is the expression of a high local incidence of the disease and a maximal incidence of other aetiological factors.

In Samoa, where the incidence is said to be 100 per cent, it is stated that 100 per cent of children are infected before the age of two years. In Jamaica it is stated that 91 per cent of the cases are infected before the age of fifteen years, 96 per cent before twenty, and 60 per cent during the first four years of life. In another group the peak of incidence was at seven years and this was then found to correspond with the beginning of school life, showing that special factors may come into play at particular ages in selected groups. It was also shown that the 'rate of infection', i.e. the numbers of persons acquiring yaws per 100 non-

immunes of the population for a given length of time, in a given age-group, was greatest for the age-groups 5 to 9 years and 10 to 14 years, the ages when the chances of skin trauma and bodily contact are greatest.

(3)—Importance of Trauma and Insect Vectors in Transmission

Abrasions of the skin probably constitute the chief factor disposing to infection with the treponema of yaws, liability to skin trauma being bound up with absence of clothing and the mode of life. In most cases probably the infection is direct from a patient with infective lesions.

On the other hand, that the infection may be carried by insects has long been suspected, and recent work in Jamaica and elsewhere suggests that this method of transmission possibly plays an important part. E. Bancroft as long ago as 1769 believed that flies transmitted yaws. Schilling (1770) suggested that in Surinam the infection was carried by a small fly which was known locally as the 'yaws fly'. Wilson in 1869 again referred to the probability that flies are responsible. L. Sambon drew attention to *Hippelates flavipes* as a possible carrier in the Antilles; van den Barne suggested *Stegomyia*. L. Nicholls (1911) in the West Indies believed that a fly he referred to as *Oscinis pallipes*, but since identified as *Hippelates flavipes*, carried the infection to injured skin surfaces. P. K. Wilson and A. W. Mathis thought that *Hippelates pallipes* played the part of intermediary in Haiti; Gonzago suggested that *Culicoides* so acted in Brazil. Hurst and Johnson were inclined to incriminate the plague of flies which appeared at the season when the bread-fruit rots in Samoa. T. von Bulow (1925) in Costa Rica, noting that 87 per cent of the primary lesions were on the lower limbs, put forward the idea that the tick *Amblyomma cayennense* might be involved.

Very few attempts at experimental transmission by insects have been made. A. Castellani (1907) made experiments in Ceylon to show that mechanical transmission of the treponema by *Musca domestica* was possible. J. G. Thomson and W. A. Lamborn (1934) showed in Nyasaland that *Musca spectanda* will feed voraciously on yaws lesions and that *Treponema pertenue* passes rapidly, in viable form, through the fly's alimentary canal and may easily thus be deposited on an abrasion of the skin of another person. More recently Lamborn (1936) demonstrated that *Musca sorbens* may deposit its 'vomit-drop' containing *Treponema pertenue*, from a previous feed, on an experimental skin abrasion in man 35 to 50 minutes later and thereby produce infection.

In Jamaica the Yaws Commission produced evidence that the distribution and incidence of yaws in that country were possibly determined by the presence of the small fly *Hippelates pallipes*, the distribution of which in turn appears to depend on geographical configuration and rainfall. The female fly feeds in enormous numbers on yaws lesions, preferably those on the lower extremities, and takes in large numbers of treponemas which remain motile for a considerable time in the oesophageal diverticulum, reappearing at intervals in the 'vomit-drop'.

It was later experimentally demonstrated that if these flies were then allowed to feed on a granulating wound on the back of a rabbit or a scarified area of its scrotum, infection resulted. A further point of interest came to light: positive results were much more commonly obtained if the experiments were made in the winter months or if the animals were removed to a cool climate after inoculation for the period of incubation.

(4)—Causal Organism

The causal organism of yaws, *Treponema pertenue* (*Spirochaeta pertenue*), is morphologically indistinguishable from *Treponema pallidum* (*Spirochaeta pallida*) and *Spirochaeta cuniculi*. All the methods of staining commonly used for *T. pallidum* are applicable to *T. pertenue*. It is stated that the latter has been cultivated by the same method as that adopted for the former but subsequent transmission to animals has not been carried out successfully. *T. pertenue* is easily demonstrated in fresh preparations from active yaws lesions by dark-ground illumination (see SYPHILIS, Vol. XI, p. 537). The duration of survival after removal from the body is short and infectivity disappears quickly.

Though the organisms of yaws and syphilis appear identical, they are considered to be differentiated by their biological reactions. There is a difference of 'organotropism' or tissue selectivity; *T. pertenue* is said to be ectodermotropic, *T. pallidum* mesodermotropic; the former is less 'invasive' than the latter.

Monkeys, rabbits, guinea-pigs, and mice may be experimentally infected with *T. pertenue*; certain differences between experimental infections due to *T. pertenue* and to *T. pallidum* have been described which will not be further detailed here, except to say that they are considered to be characteristic in the two cases and a sufficient basis upon which the two organisms may be differentiated.

3.—MORBID ANATOMY AND SEROLOGY

Histo-pathology of the skin lesions

The structure of a yaw consists essentially of a plasmoma of the cutis with marked hyperplasia of the overlying epidermis, hyperkeratosis and parakeratosis. There is marked upgrowth of the papillae and a corresponding downward prolongation of the rete. The papillae may be from ten to twenty times their normal length and also enlarged in other dimensions. The rete pegs are not increased in number but they vary in thickness and length and in places appear to cut off parts of the papillae into islands (acanthosis). The suprapapillary layers may appear insignificant in comparison to the thickened rete. The palisade layer of basal cells remains normal, the columnar cells forming a rather well defined boundary between the epidermis and corium, though here and there the cellular invasion of the latter may break through its proper continuity and make contact with the rete.

In the epidermis, immediately above the basal layer of cells, changes are visible. In the middle of the down-growths oedema is present; many cells, which may have preserved to a large extent their prickly boundaries, have lost all vestiges of their nuclei and many are vacuolated (spongiosis). In some areas larger tracts exist in which cell envelopes only can be made out, or all cellular outlines have disappeared and only an occasional nucleus can be distinguished. *Epidermis*

Superficially to the rete one of two conditions may be found—either a layer of ten or more strata of ill-defined almost circular granular cells, topped by swollen hyperplastic almost homogeneous horny cells, or the stratum granulosum, which is largely indistinguishable, is surmounted by a thick dense stratum corneum infiltrated with masses of mononuclear cells. The horny layer may be split into lamellae and contain fibrinous coagula. They form in part the crust. *Superficial layers*

Not uncommonly circumscribed areas may be seen, lying nearer to the surface than to the basal layer, containing leucocytes (pus cells) and detritus. These are of the nature of miliary abscesses and within them the treponema can be demonstrated. The framboesial nodule or raspberry-like lesion after removal of the crust is covered with only a suprapapillary layer of prickly cells.

The epithelial growth rests upon a solid cellular infiltration of the cutis made up of all types of cells but chiefly of plasma cells. These surround the individual epithelial processes like a mantle, extending in thin cords into the papillae, and below the level of the epithelial down-growths the infiltration forms a uniform plasmomatic layer occupying the outer half of the corium sharply limited below by a horizontal line. There is some oedema of the corium, the collagenous tissue in the infiltrated area is reduced to a fine network, and the veins in the area are engorged. The blood-vessels of the papillae are dilated and there may be some infiltration with lymphocytes but the vessels do not show productive inflammation with thickening. The intima remains intact without any cellular infiltration, nor any more endothelial proliferation than may occur in any inflammatory process. There is some loss of pigment; giant cells are rarely and hyaline degeneration is never seen. The skin appendages are not affected. *Dermis*

In early lesions treponemata are found in large numbers in the perivascular tissue about the terminal portions of the papillae and in some of the rete pegs, deposited there by the blood-stream. From this initial lesion they pass into the more superficial layers of epithelium. Organisms are rarely found in the subpapillary dermis. Although they may be seen in close association with cells of all kinds, they are not seen within any cell in the rete Malpighii. *Distribution of treponemata in lesions*

In the lesions of the palm of the hand and sole of the foot, referred to below (see p. 647), the structure is essentially the same but the changes are mainly in the horny layer which may be five to ten times the normal thickness. The outlines of the individual cells are obliterated so that this layer comes to be formed of a homogeneous stratum of keratinized *Lesions on palm and sole*

material. Here and there lying in a kind of nest embedded in the hyperkeratotic horny layer but separated from it by looser layers of cells and spaces, the little pegs called 'clavus' are found. They consist of laminated horny cells interspersed with parakeratotic cells, are more or less rounded and project slightly above the surface of the skin, and are easily shelled out of their nests leaving the 'nail hole' which reaches almost to the rete. The stratum lucidum is easily made out; the granular layer is thickened some three to eight times. There is no infiltration of the rete, and miliary abscesses are not found. The acanthosis is not so marked as in the more active lesions. Some of the papillae are enlarged and some flattened; oedema is present in the papillary and subpapillary layers. The infiltration is practically confined to the papillary layer and the region of the blood-vessels and is composed mainly of plasma cells.

Serology

The Wassermann, Kahn, and other similar tests used in syphilis all yield positive reactions in yaws, up to 100 per cent. The Wassermann and Kahn reactions give a 90 per cent agreement in yaws, but the latter is the more sensitive in latent cases. Reactivity of the serum begins in the early secondary stage and is maximal when the secondary eruption is widespread and well developed, but a positive blood Wassermann reaction has been recorded in Jamaica within two weeks of the appearance of the initial lesion. It persists through long latent periods and is present in old cases of yaws showing persistent lesions, though in those with tertiary manifestations it may be diminished. There is reason to believe that consequent upon natural cure, following a florid secondary exanthem or after treatment, reactivity may disappear. The exact treatment which will determine the return and persistence of normal non-reactivity has never been decided. It will depend in part upon the extent and duration of the secondary eruption at the moment when treatment is instituted. Reactivity may continue to diminish after treatment has ceased and may become negative long after the lesions have disappeared. Although in some 60 per cent of cases with infective lesions the Wassermann reaction may be reversed by a course of treatment, the same result will only be obtained in 30 per cent of latent cases by the same treatment.

The complement-binding strength of titrated serum from cases of yaws is equal to the maximal strengths of syphilitic sera. Whether there is any constant difference in the time which elapses between the date of infection and the date when partial complement-fixation begins in yaws and syphilis has never been shown. Whether the titre curve runs the same course or not in both diseases is not known, either in treated or untreated cases. Titration curves worked out recently in Jamaica showed that after treatment by arsenicals or bismuth there was in general a gradual decrease in the average Wassermann titre extending over approximately five months but with a tendency to an interruption in the fall in the third to fourth month. After the first six months the percentage of positive Wassermann reactions tends to rise. Of 73 patients

recorded in Jamaica who had received a short course of neoarsphenamine five years before, 33 gave a negative Wassermann reaction, 11 a doubtful result, and in 29 the reaction was positive. Certainly late cases, even after long courses of treatment, may preserve a positive reaction.

Immunity

Clinical and epidemiological observations suggest that those who suffer an attack of yaws develop a serviceable immunity. In native communities it is generally believed that one attack protects against subsequent infection, an opinion shared by many medical men. It is believed that immunity develops more quickly and in higher degree the more florid the secondary eruption and the greater its distribution over the body. Interruption in the course of the disease in this phase by treatment hinders the development of immunity. The whole subject has been complicated by the introduction of the conception of what has been termed 'infection immunity' in syphilis and its extension to yaws. This hypothesis suggests that so long as an infection with a particular organism exists, the body remains immune to reinfection but that once the body is completely cleared of the infecting organism susceptibility returns, but it fails to take into account many essential facts and is in all probability considerably wide of the truth.

Experimental work on monkeys carried out in the Philippine Islands suggests that the immunity in yaws, as demonstrated by failure to infect on reinoculation, is a real immunity, that it develops only after the infection has lasted some considerable period, and that once produced it remains for life. In monkeys, successful super-inoculation may be possible for the first seven months in yaws, in contrast to syphilis in which positive results were only obtained during the first six weeks. Thereafter, in both diseases further inoculations fail to cause inoculatory lesions. Reciprocal immunity between yaws and syphilis and between syphilis and yaws in monkeys has been demonstrated, but syphilis produces immunity to syphilis more quickly than does yaws to yaws. With a high-grade homologous immunity heterologous immunity occurs; it develops later but may be complete in these animals. After immunity has been produced, the organisms introduced by super-inoculation fail to multiply and in high-grade immunity are completely suppressed. All the secondary lesions may have healed while susceptibility to super-inoculation persists and alternatively lesions may remain long after susceptibility to reinoculation has been lost.

*Experimental
work on
monkeys*

It would obviously be unwise to apply the results obtained by animal experiment to man, however suggestive they may be. Experimental research on man has been so far very limited; the factors involved are numerous and again any conclusions that may be drawn must still remain tentative. The results of work carried out recently in Jamaica, using non-reactivity to experimental super-inoculation as the sign of immunity, suggest that immunity to an homologous strain of *Treponema pertenue* (auto-inoculation) develops early in the course of a natural

*Immunity in
man to
homologous
strains*

yaws infection and that such immunity persists throughout the course of the active stage of the disease. Immunity to heterologous strains develops slowly over a number of years; 90 per cent of cases of yaws in which the duration of the infection has been less than three years may still be successfully reinoculated. If the disease in the eruptive stage is interrupted by treatment immunity is long delayed.

Whether patients with yaws who have developed an immunity to successful reinoculation with yaws are immune to syphilis has never been determined experimentally. On the other hand it is known that general paralytics are usually resistant to inoculation with yaws. The epidemiological evidence concerning cross-immunity is conflicting. It has been held that syphilis does not occur in certain yaws communities on account of the 100 per cent incidence of the former conferring an immunity to the latter. This, however, has never been proved and certainly in other communities wide-spread yaws has not been a bar to the introduction of syphilis.

The apparent exclusion of one disease by the other is well illustrated in Nigeria but there, as elsewhere, it will probably be found to be apparent only and that it is the presence of other factors which determines the presence of one or the other infection.

Other blood changes

There is no anaemia and there are no changes in the leucocyte formula in uncomplicated yaws. A low blood-cholesterol content has been demonstrated in the disease as in syphilis. The globulin precipitation test with distilled water has been found to be positive in at least a 1:3 dilution, sometimes 1:1 in active cases. The reaction appears in the stage before the Wassermann reaction becomes positive, is less marked in latent cases, but persists after the Wassermann reaction has become negative with treatment. The yaws curve does not therefore run parallel with the Wassermann curve.

4.-CLINICAL PICTURE

In the past the symptoms of yaws have been described as occurring in three stages, comparable to those described in syphilis. This method of presentation in syphilis has been found to need many modifications and in yaws it is still less applicable as there are not any clear-cut divisions into primary, secondary, and tertiary stages. However, with this proviso, the old method of designation will be followed.

The incubation period, i.e. the time which elapses between a naturally occurring infection and the appearance of the primary lesion, remains a little uncertain. It varies probably in most cases between three and six weeks with limits of two weeks to several months. In experimentally induced infections in man typical primary yaws yielding treponema develop in three and a half to four weeks. During this period symptoms

are as a rule absent, the prodromal symptoms, which have been described by some writers, belonging more properly to the secondary stage.

The primary lesion—'mother yaw', 'maman pian', or 'madre buba'

The site of the primary yaw is determined to a large extent by liability to trauma and may vary in different groups of cases. The location of the primary lesion does not appear to influence the course of the disease. In bare-legged unbooted native races the initial sore occurs on the lower limb below the knee in 50, 70, or 90 per cent, and is so located in males more often than in females in about the proportion 85 : 75. The ankle and foot are involved nearly twice as often as the leg, and the anterior aspect of the leg more commonly than the back. The initial lesion may be on the face and neck in from 5 to 10 per cent in various series of cases, on the trunk in about 9 per cent, on the upper limb in 5, 10, or 20 per cent, and on the genitalia in under 1 per cent. Among women who acquire the disease in adult life, infection is gained quite commonly from their own children by suckling, the primary lesion being on the nipple. In a series of cases in which both mother and child suffered from active yaws, the disease was contracted by the mother from her child in 75 per cent and the converse in 25 per cent.

*Site of
primary yaw
in native
races*

In contrast to these figures for natives in their natural surroundings are those recorded in the outbreak of yaws among Johannesburg miners. Primary lesions were found on every part of the body except the lower part of the leg, the ankle, and the foot, a fact explained by the habit of these men of working divested of most of their body clothing but never of their socks and boots.

*Site of
primary lesion
in miners*

The primary lesion occurs at the site of inoculation, the organism gaining entrance by any breach of the skin surface; thus abrasions, cuts, insect bites, the vesicular dermatitis on the feet known as 'ground itch' due to ankylostome infection, vaccination scarifications, and leech bites may all form portals of entry for the treponema. The organism may also be implanted upon an ulcer due to other causes and the primary yaw run its course independently of the ulcer.

It has been stated, and the statement repeated with descriptive embellishments, without regard to the facts, that the primary lesion may appear as a vesicle or as an ulcer. The primary lesion is not an ulcer; it appears first as a papule and then develops into a nodular granuloma. How these mis-statements arose is not very clear but they may be due to a wrong interpretation of the French word *ulcère*, which is used in a wider sense than the English word to include nodular as well as ulcerative lesions. In some cases the primary lesion is so small and undergoes retrogression so quickly that it passes unnoticed, in others indeed it seems probable that no visible lesion appears at the point of inoculation. Typically, however, the tiny papule develops in a few days into a small nodule and later into the characteristic crust-covered papillo-granuloma which projects from the skin surface.

*Primary
lesion*

The covering is at first thin, tough and leathery, dry, and yellowish-grey,

rmly attached at the periphery but separated from the granuloma beneath by a drop of thin yellowish sticky muco-pus. If the crust is removed a fresh one is formed by the honey-coloured fluid which oozes from the lesion beneath, or if the original covering has become split or partially detached the exudate forms a matted crust with it. The lesion when uncovered presents as a moist pinkish-red raised papillo-granuloma, sometimes exhibiting minute bleeding points.

The fully developed primary yaw may vary considerably in size and in some cases reaches enormous proportions; the diameter may be from 1 to 6 cm. When situated on the lower extremity it tends to be much larger than when it occurs elsewhere.

In certain situations the lesion may undergo modification; thus on warmer and moister areas of the skin, as in the axilla and about the pudenda and perineum where the skin surfaces are opposed, the crust gets rubbed off and the lesion becomes flattened and moist, with a mushroom-like appearance, an overhanging edge, and depressed centre. In other parts the crust may fall off and the granuloma become dry and warty with marked hyperkeratosis, heaping up, and exfoliation of the surrounding skin, most commonly seen when the mother-yaw develops on the foot. When the primary lesion develops in an already existing ulcer it tends to grow large and may fungate, just as a primary lesion produced by experimental inoculation of a granulating wound is much larger than one following inoculation of the skin. If such a case be submitted to treatment the framboesial granuloma will disappear and the ulcer remain *in statu quo*.

The primary yaw may heal in a few weeks and have disappeared before the generalized eruption becomes manifest or it may retrogress spontaneously as the metastatic eruption is developing. More commonly it lasts for many months and may outlive the secondary eruption and persist for many years.

When the primary yaw heals, scarring tends to be more prominent than is the case with secondary lesions, partly probably because traumatization and secondary infection are commoner in the former. The colour of the scar in coloured races is sometimes said to be white, in distinction from the scars of the secondary lesions, which are pigmented. This, however, is not essentially true; it is a question of whether there has resulted loss of tissue due to secondary infection of the primary yaw, or maltreatment, e.g. by cauterization.

Accompanying the maturation of the initial lesion there is often a satellite bubo in the group of lymphatic glands draining the part. In this gland treponemata can be demonstrated, suggesting a dissemination by lymphatics before invasion of the blood-stream occurs. In a single case small nodules are recorded to have developed along the course of the lymphatic vessels between the lesion and the gland two weeks after the appearance of the initial lesion and one month before the secondary eruption occurred.

The secondary stage

About one to three months after the development of the primary lesion the generalized or secondary eruption appears, in some cases ushered in or preceded by constitutional disturbance of varying severity consisting of fever, malaise, headache, and aching pain with exacerbations at night in the back and in the long bones and joints of the limbs. *Constitutional symptoms*

Some writers have laid stress upon the polymorphism of the skin lesions of the secondary stage, perhaps rather unnecessarily, as all the several types of eruption have essentially the same structure and only differ in magnitude, evolution, and grouping. The whole gamut of syphilological nomenclature has thus been introduced, and lesions have been represented as being roseolar, papular, macular, follicular, nodular, papulo-erosive, papulo-squamous, papulo-pustular, lichenoid, exfoliative, psoriasiform, keratoid, corymbiform, framboesiod, condylo-matoid, or verrucose. Metastatic yaws, however, differ in no essential way from the primary yaw. Their number may vary from less than half a dozen lesions to many hundreds scattered over the whole body. They tend to be more numerous in males than in females. *Skin lesions*

The individual secondary lesion commences as a discrete tiny flat reddish papule with a corrugated surface. As this develops to the size of a split-pea it is seen to be covered by a tiny yellowish crust. Many such lesions may remain unchanged for weeks and then disappear, or they undergo further development into typical framboesiform lesions. In perhaps 1 per cent of early cases this papular eruption may occur alone; in cases exhibiting the typical efflorescence papular lesions will be found, if looked for, in about 12 per cent. The papules may be observed in all stages of evolution and retrogression. In some cases they tend to form more or less closely knit groups scattered over the face, body, and limbs; in others the massed micropapules with slightly corrugated surface and scale formation have the appearance of a lichen. Sometimes hyperkeratosis is more marked and the papules resemble the folliculo-papules of lichen pilaris. Again, macules may occur, chiefly on the back, less commonly on the abdomen and limbs, 1 to 3 inches in diameter, the elements of which consist of minute conical folliculo-papules. These patches are oval, rounded, circinate, or irregular in shape as the result of coalescence, the margin is slightly hyperaemic, and in colour they appear paler than the surrounding dark skin. They are rough to touch and feel like goose-skin or a nutmeg-grater.

Reference is often also made to the furfuraceous desquamation, seen not uncommonly in yaws patients about the time of the secondary eruption, associated with a loss of the natural gloss of the skin, which becomes dry and rough. That it is a manifestation of yaws has been denied by some observers who hold that among those natives who continue to care for their skins and to use oil inunctions it is not seen. On the other hand, most observers believe the condition to be due to yaws; it may have a patchy distribution and, after persisting for some *Desquamation*

weeks, clear up. The powdery desquamation is due to the formation of lightly packed minute scales, each probably representing a unit yaws lesion. In these areas papular and framboesiform lesions may develop. The patches resemble somewhat a tinea versicolor infection on a black skin. The secondary eruption in yaws may be pruriginous or this symptom may not be observed.

Papular and macular eruptions may precede, accompany, or follow the main eruption; treponemata may be demonstrated in all. The evolution of the typical secondary yaw is precisely the same as that described for the primary lesion. In size they may vary from a pin's head to half a crown but they seldom attain the dimensions reached by the mother-yaw. Secondary lesions known as daughter-yaws or satellite yaws may occur early, surrounding the initial sore. Also an efflorescence of papular lesions may surround a secondary yaw to form a constellation. Groups of framboesiform lesions may fuse to form more massive growths; by a process of partial retrogression or healing a condition which has been called 'ringworm yaws' may be produced.

A secondary yaw reaches maturity in from two to three weeks; fresh crops may continue to appear at intervals of weeks or months for a year or so; the disease may then appear to come to an end but any one of these different types of generalized eruption together with typical framboesiform lesions may appear, disappear, and reappear for twenty years or more after infection. It has been recorded that 2.5 per cent of cases infected twenty years previously showed infective lesions. The lesions are the same whether they occur in a bush native or in a town-dweller, in white or black. In any group of actively infective patients those with framboesiform lesions will form 85 to 96 per cent of the total. On the other hand in a total population 100 per cent infected with yaws in all stages, only a minority will show the typical secondary yaws eruption.

The various forms of the secondary eruption have been reproduced in experimentally inoculated yaws. Abortive lesions, such as may be seen in natural infections, tended to occur in reinoculated persons and there is evidence that they are a sign of a partial immunity.

The distribution of the secondary eruption may vary considerably; when the number of lesions is small they tend to be situated on the warmer and moister parts of the skin, as has been remarked in the colder mountain endemic areas. When the lesions are numerous and the whole body is involved, a greater proportion will be found upon exposed parts: the face, the anterior surfaces of the body and limbs, with a special grouping about the orifices, mouth, nostrils, vulva, and anus. Onychia and paronychia may be seen. The scalp is commonly spared. A secondary yaw, like a primary lesion, situated in a moist warm part becomes a moist lesion and resembles closely a syphilitic condyloma. An intercurrent febrile affection may cause a temporary disappearance of the secondary efflorescence.

As in other diseases, irritation of skin surfaces and trauma may

determine the distribution of lesions and the common affection of the hand and foot may thus be accounted for. Owing to the special characters of the skin of the palms and soles, these lesions tend to take on rather special features. In the case of the sole of the foot, in consequence of the thick dense epidermis the yaw may extend laterally and reach considerable size, causing much suffering, before the epidermis gives way and splits. Such a lesion is usually accompanied by marked hyperkeratosis with great thickening and exfoliation in the neighbourhood and goes by the name of 'foot yaws' or 'crab yaws'. The condition is a source of much incapacity and may persist for many years. In a group of 500 patients showing infective lesions 42 per cent presented only plantar yaws—47 per cent of the males and 35 per cent of the females. In other cases, multiple lesions of the sole of the foot undergo hyperkeratosis and dry up leaving hard centres which eventually fall out leaving 'nail holes', the condition being known as 'clavus'.

Lesions on feet

'Crab yaws'

Clavus

The palms of the hands may be the seat of lesions comparable to those in the soles of the feet. Papules developing in the deeper layers of the epithelium may push their way to the surface with splitting of the epidermis and marked hyperkeratosis, or the lesions may be macular in type. In some cases hard rounded or flattened nodules appear with thick hard epidermal plugs in the centres which, as in the case of the feet, fall out leaving a condition which was originally described as 'the peculiar pitting of the palms'. In other cases a general thickening of the epidermis with hyperkeratosis, cracking, and fissuring may be the only obvious affection of the palms of the hands and soles of the feet. This may begin in one area and spread peripherally reaching the sides and dorsa of the hands and feet or it may be only noticeable over the joints of the fingers, hand, wrist, and toes.

Lesions on hands

The condition is often associated with pigmentary changes; irregular areas with scalloped margins develop showing all degrees of depigmentation and in adjacent areas hyper-pigmentation may be noted. These pigmentary changes extend on to the forearm and over the ankles but seldom reach the elbow or knee. They were first described by a German observer as a form of leucoderma under the name *Melung*.

Pigmentary changes

'Melung'

A mild keratosis of the skin over the shins and elbows has also been described. The keratoid affections of the hands and feet tend to occur late in the secondary period and to persist or, like other secondary lesions, they may develop after a long latent period. It is on this account that they are often included among the tertiary manifestations of yaws. As has been indicated above, they constitute the commonest lesion in a composite group of yaws cases of all ages.

Keratosis

Lesions of mucous membranes

Though many tens of thousands of cases of yaws have passed through the hands of those in charge of antiyaws campaigns, it is seldom stated in the published figures whether lesions of the mucous membranes have been observed or, just as important, whether they have been sought for

and found to be absent. It is perhaps therefore a little unwise to assert that they do not occur, though many writers, basing their beliefs on their own observations, consider that the secondary eruption is limited to the skin and never appears on a mucous membrane. The published cases, and their number is very small, as cases in which a mucous membrane has been the site of a yaw, appear to be capable of explanation along other lines; some reported as examples of mucous membrane lesions have in fact been cases with lesions situated on skin, in ignorance of the fact that the nasal vestibule, the vulva, and the glans penis are clothed with skin and not mucous membrane. One author referred to cases in which 'the mucous tissues of the ears' were affected. Many other cases have been recorded in which a lesion of a mucous membrane was stated to have been noted, when in reality the condition present was merely a spread of the lesion by continuity across a muco-cutaneous junction. These straddle or *à cheval* lesions are not uncommon about the lips and may occur at the conjunctivo-cutaneous junction. Apart from these there are a few apparently well authenticated cases in which a yaw has been discovered wholly upon the mucosa of the mouth or nose. These, however, are quite possibly not examples of the exanthem affecting a mucous membrane but the result of direct inoculation by trauma, in the case of the nose by 'picking' the nose and in the case of the mouth by the teeth or rough food.

Tertiary stage: tertiary lesions of skin and bone

The lesions now to be described are usually spoken of as tertiary manifestations of yaws but though a latent period of many years may elapse before they appear, many if not all of them may occur quite early in the course of the disease, more often perhaps towards the end of the secondary stage. Just as many of the abortive skin lesions may be looked upon as evidence of a developing immunity, these so-called tertiary manifestations may be considered as evidence of the onset of sensitization or allergy. Tertiary lesions appear to be more common in patients in whom the secondary eruption has been ill-developed and less common in cases in which a florid exanthem has occurred. In some cases, probably in more than is usually suspected, a persisting primary or secondary lesion undergoes a change; there is a change in tissue reaction, breaking down occurs, and it takes on the character of a tertiary lesion. This change may occur at any interval from one to twenty years after the original appearance of the lesion.

In other cases nodules form in the skin and subsequently break down with the formation of gummatous-like ulcers, practically indistinguishable from those of syphilis. An ulcer may remain localized or spread widely over a large area leaving in its wake subsequent extensive scarring, often producing marked deformity. Instead of this more superficial type of creeping ulceration, the process may invade the deeper tissues and involve the bones. This attack upon bone from without must be distinguished from the other common tertiary manifestation of

yaws consisting in a primary osteitis, osteo-periostitis, or epiphysitis, to which may be added bursitis, teno-synovitis, and arthritis.

Bone pain, as has already been pointed out, is common and often severe in the secondary stage and probably signifies a localization of the treponemata in osseous tissues. If the secondary eruption is profuse it appears possible that a true immunity may follow and no further development of the organisms take place. On the other hand in some proportion of cases, perhaps 10 to 20 per cent or more in some endemic areas, demonstrable lesions of bone occur, probably of the same nature as those that occur in the skin. In these late lesions treponemata are not found. As in the case of the skin, bony changes may appear in the latter part of the secondary stage, even when the primary lesion still persists, from six months to six years after the initial lesion appeared. In nearly 50 per cent the bone lesion begins within twelve months of the primary sore. In any group of yaws cases some 50 per cent of those with bone lesions will be under fifteen years and 75 per cent under twenty years of age.

Bony lesions are multiple in three-quarters of the cases and may number a hundred or more. In some the affection involves practically the whole skeleton. The long bones show the highest incidence; the tibia is affected in 40 per cent, the phalanges of the hand and foot each in 30 per cent, the metatarsals, metacarpals, and radius each 20 per cent, the humerus and patella each 15 per cent, the ulna and femur each 10 per cent, and the ribs, sternum, tarsus, carpus, and pelvis each 5 per cent. The calvarium appears to be occasionally involved and it may be said that no bone is exempt (see goundou, p. 654). The shaft of the long bones is attacked four times more often than the epiphysis. The apparent disposition of children and young adolescents to develop bone lesions may possibly be associated with poor feeding and unbalanced diet. Serial routine radiological examinations of a large group of early cases of yaws would probably show a higher incidence still and yield without doubt a good deal of much needed information concerning the evolution of these osseous reactions.

Several types of bony lesions have been described on clinical, radiographical, and necropsy findings but their relation to each other and their pathogeny is still somewhat doubtful. The symptoms accompanying the acute cases in young children are fever, local aching, pains worse at night and increased with any attempt at movement, tenderness, and sometimes swelling and shiny skin.

The X-ray appearances have been described as characteristic: oval areas, with the long axis in the axis of the bone, 1 to 30 mm. across, of lessened density are seen either within the substance of the cortex or cut into the surface of the bone, giving the appearance of pieces of the bone having been gouged out. The periosteum may be destroyed over these areas or it may be thickened and raised; there may also be some general rarefaction of trabeculae and loss of cancellous tissue giving the picture of osteoporosis, or there may be thickening of the cortex with

*Distribution
of bone
lesions*

*Radiographical
appearances
of lesions*

increased density according to the stage of evolution of the process. These areas may be few or many and scattered all through the bone. They may apparently undergo resolution with restoration of the osseous tissue or they may break down with the formation of fistulae. Some of these lesions as seen in radiographs may correspond to the clean-cut smooth hollows to be seen in dry bony specimens.

In contradistinction to these focal lesions a diffuse type of osteitis may be seen involving the whole or some part of the shaft with its periosteum. The whole thickness of the cortex takes part in the process; the circumference of the bone is increased and the medullary cavity is narrowed. The periosteum presents irregular thickening or node formation and the trabecular architecture of the marrow is disturbed. During the acute inflammatory stage the bone is softened, and bowing, most prominent in the tibia and less often in the femur, may follow, the tibial deformity resulting in the 'sabre tibia' of yaws—the 'machet leg' of the Congo or 'boomerang leg' of Australia. Later the acute phase may come to an end and resolution take place, the tibial deformity, however, persisting with a still thickened cortex. Later still the bones may assume a more normal texture though the curvature remains. In other cases irregular thickenings of the bone persist, breaking down occurring with the formation of fistulae and ulceration of the skin. These processes may attack the epiphyses and joints and be associated with a hypertrophic synovitis, teno-synovitis, and bursitis leading to ganglion formation about the wrists, ankles, and elsewhere.

The destruction of tissue may be very great, incapacity severe, wasting of muscles extreme, and cachexia profound. With atrophy of parts of the limbs, ankylosis of joints, gross scarring, and conditions resembling elephantiasis or mycetoma, the most grotesque deformities are produced.

Visceral lesions

In connexion with the primary yaw, enlargement of the lymphatic glands draining the part may occur and a more generalized lymphadenitis may be seen in the secondary stage. Glands become infected within two weeks and treponemata can be recovered from them. After the skin lesions have healed, treponemata are said to disappear from the glands; suppuration never takes place. That a generalized blood infection must occur appears to be indisputable; treponemata have been demonstrated in the splenic blood of man and in the peripheral circulation and bone marrow of experimental animals but visceral lesions in man have never been proved to be caused by the organism of yaws. In the present state of knowledge this would obviously be difficult.

Some observers, however, believe in a framboesial aetiology for a number of conditions occurring among native patients which are elsewhere known to be caused by syphilis, such as general paralysis, tabes dorsalis, hemiplegia, paraplegia, aneurysm, and kerato-iritis. In the records of such cases a clear distinction has very often not been made

between the subject of parenchymatous nervous disease and cases exhibiting nervous symptoms due to vascular lesions. Recently in Jamaica an attempt has been made to correlate the indirect evidence of an association between yaws and 'nervous lesions'. It was found that the yaws incidence among the total population of 57,000 was 56.6 per cent; among 100 collected 'neurological cases' it was 80.0 per cent; or, put another way, there were 1.2 neurological cases per 1,000 non-yaws inhabitants and 2.5 per 1,000 cases with indications of former yaws. The total population, however, includes all ages, whereas neurological cases occur among adults. It is not certain therefore that the incidence of neurological cases among non-yaws adults was any lower than among yaws adults. Of the neurological cases 89 per cent had had yaws or a positive Wassermann reaction. The series included: 27 cases of hemiplegia, 22 with a history of yaws plus 3 with positive blood-Wassermann reaction; 21 cases of paraplegia, 19 with a history of yaws plus 2 with positive Wassermann reaction; 4 cases of general paralysis, all with history of yaws; 13 'tabetics', 9 with a history of yaws plus 4 with positive Wassermann reactions; 5 cases of facial paralysis, all with a history of yaws. Four patients gave a history suggesting syphilis, one of these was a paralytic who also had a history of yaws: the second and third were cases of hemiplegia and tabes dorsalis respectively in whom the Wassermann reaction was negative and there was no history of yaws.

Such evidence may be suggestive but that is all that can be said. Yaws might, in such cases, be merely a disposing cause or, as has been suggested elsewhere, a yaws infection might mask a subsequent syphilitic infection, which symptomless latent infection might later give rise to neural and vascular lesions.

The cerebrospinal fluid has been examined in some small series of *Cerebrospinal fluid* uncomplicated cases of yaws. The Wassermann reaction has always proved negative in the secondary stage. In some very few cases a slight increase in protein and cells has been noted. In the absence of controls these findings cannot be definitely associated with the yaws infection. In 61 of the 100 Jamaican neurological cases the cerebrospinal fluid was examined and found normal in 43 and abnormal in 18. Among those with normal fluids the blood-Wassermann reaction was positive in 42 per cent; among those with abnormal fluids in 83 per cent. Of the 18 cases with abnormal fluids the deviation consisted of: positive Wassermann reaction in 13 (with normal mastie curve in 6, abnormal in 7); abnormal mastie curve only in 2; increased cell count (14 cells) only in one; and positive Pandy test in 1. In three-quarters of the cases with hemiplegia the blood-Wassermann reaction was positive. In 13 of the 22 the cerebrospinal fluid was examined and found normal in 9 and abnormal in 4 (positive Wassermann reaction in 3, positive Pandy test in 2, and an abnormal mastie test in 1).

The blood-Wassermann reaction among 18 cases of paraplegia was positive in 12 and negative in 6. In 15 of the 18 cases the cerebrospinal

fluid was examined and found normal in 10 and abnormal in 5 (positive Wassermann reaction 3, cell increase 1, abnormal mastic test 1).

There were 9 cases of tabes with yaws: the blood-Wassermann reaction was positive in 5 and negative in 4. In 7 cases the cerebrospinal fluid was examined and found normal in all. Of the 4 cases of general paralysis the blood-Wassermann reaction was positive in 2 and negative in 2; all yielded abnormal cerebrospinal fluids (1 a positive Pandy test only; 1 showed increase in cells, positive Pandy test, positive Wassermann reaction and mastic curve; 1 a positive Wassermann reaction, cell increase, positive Pandy test, and abnormal mastic curve; 1 a positive Wassermann reaction and an abnormal mastic curve).

Such cases, occurring in a community wherein yaws is rife but syphilis cannot be excluded though apparently rare, must await further progress in our knowledge before they can be written down as framboesial and the changes in cerebrospinal fluid as due to an infection with *Treponema pertenue*.

Three cases have recently been reported from Jamaica, in children aged 9, 5, and 2 years respectively, one with yaws of 18 months and two of 1 month duration, in whom swellings in the testis and epididymis were noted. It was considered that these lesions might be due to yaws but no proof was forthcoming.

5.—COMPLICATIONS AND SEQUELAE

Yaws does not appear to dispose to any particular complication but causes an enormous amount of invalidity and incapacity in endemic areas. The general health is undermined and wasting marked in many tertiary cases and there is a greater liability to sepsis and intercurrent infection. Stunting of growth, cancrum oris, and stricture of the prepuce have been recorded. Among the sequelae are gross scarring with keloid formation and fixation of joints and contractures. Malignant changes implanted on framboesial lesions appear to be very rare; melanomatous growths, however, have been noted on the site of old 'crab yaws', possibly due to the habit of holding the affected foot in the hot smoky flame of burning powdered resin.

Three conditions, gangosa, goundou, and juxta-articular nodules, at one time considered separate clinical entities, are now generally recognized as due to yaws, though similar if not identical affections may rarely be caused by syphilis.

(1)—Gangosa

Gangosa is a native word applied to the condition otherwise known as rhinopharyngitis mutilans in which a destructive ulcerative process attacks the pharynx, palate, and the soft parts, cartilages, and bones of the nose with the production in fully developed cases of a great hole in the middle of the face bounded below by the upper lip, which is spared in all except late persisting cases and never wholly destroyed. The pro-

cess may undergo natural arrest at any stage and before gross mutilation has occurred. In other cases the loss of tissue is very great; the process may spread up the lacrimal ducts or across the upper part of the cheek and invade the conjunctival sac and the eye. Both globes may be destroyed and the contents of the sockets be replaced by granulation tissue. In other cases the antra are involved; in a few the Eustachian tube and middle ear are affected with loss of hearing. The larynx is rarely attacked, the tongue never, and the process does not occur in any other part of the body.

Cases of gangosa have been recorded from nearly all endemic yaws *Incidence of gangosa* areas; if not recorded it does not follow that they do not occur. There is, however, a very great difference in incidence, suggesting that some second factor may be involved in the aetiology. The affection may begin at any age from early childhood onwards, though perhaps most cases come under observation in early adult life. The time which elapses between the infection with yaws and the onset of gangosa also varies, from under a year to twenty-five years. In some areas there appears to be a much higher incidence in females than in males.

Pathologically the affection is a slowly advancing necrosis with very little tissue reaction. At the edge of the lesion the epithelial layers of the skin are thickened, with parakeratosis and acanthosis; the epithelial pegs are long, thickened, and irregular, and the subcutaneous tissue is oedematous and infiltrated. In the ulcerated area the superficial stratum consists of a structureless necrotic layer lying upon a fairly defined connective tissue which shows marked infiltration with round cells and some plasma cells. There is no perivascular infiltration but the vessels are plugged with hyaline material and their walls obliterated. *Morbid anatomy* *Treponemata* have never been demonstrated in gangosa lesions, but the process is arrested by anti-yaws treatment.

The disease may run an acute course with rapid destruction or a very chronic course over many years. Arrest may occur after the process has been acute, or progress may be intermittent. The general health usually remains remarkably good. There appears to be an association between gangosa and the previous presence of yaws lesions about the nostrils and lips. The condition begins with symptoms of nasal obstruction, coryza, or sore throat associated with dull pain and itching deep to the nose and a sensation of dryness. Congestion and infiltration of the mucosa and some swelling of the bridge of the nose externally may be noticed; in others the first obvious lesion may be a dirty sloughy superficial ulceration on the pharynx or palate. Progressive destruction of the parts then goes on, in many cases with a minimum of obvious ulceration. In others there may be a good deal of foul-smelling mucopurulent discharge. *Clinical picture*

(2)—Goundou

Goundou is the name given to a condition in which hard paranasal swellings appear. They are usually bilateral and symmetrical, varying

in size from a bean to an orange. They spring from the ascending or nasal processes of the superior maxilla. First noticed when perhaps the size of a haricot bean, they may grow rapidly or more slowly and become arrested at any stage of enlargement. The geographical distribution of the condition appears to correspond roughly with that of yaws as far as records go but the incidence in endemic areas appears to vary considerably; the condition is common in West Africa but rare in Indo-China.

Actively growing specimens show an outer shell of bone covered by a thickened adherent periosteum and within a richly vascular fibrous substratum showing a feebly inflammatory reaction in which irregular lamellae of bone, areas of plasma-cell infiltration, and collagenous sclerosis are seen. The process is a low-grade inflammatory osteogenic hyperplasia. Treponemata have never been demonstrated in this tissue. When the active process comes to an end the signs of inflammation disappear, the tumours become hardened, and the covering periosteum normal.

The onset is usually in early childhood during the attack of yaws or soon after and it is not uncommonly associated with sabre tibia or a more generalized framboesial osteitis. In a few cases the onset has been after a latent period of some years. Goundou is never congenital as was at one time suggested. Associated with these paranasal swellings there may occur an osteitis of the whole of the maxilla, and any or all of the bones of the face including the mandible may be similarly involved with the production of gross deformities, resembling in some cases those of leontiasis ossea. In some cases actual goundou may be absent but a tumour the size of an orange may grow from the palate and present at the mouth. Suppuration never occurs.

A somewhat similar condition may possibly result from a syphilitic osteitis. Goundou-like swellings may occur among white races in cases which are diagnosed as leontiasis ossea or osteitis fibrosa; they may be seen in osteitis deformans, and somewhat similar paranasal bony growths are found in some animals, notably apes, monkeys, and equines. The very variable incidence of goundou in man suggests that some other factor may play a part in its aetiology.

(3)—Juxta-Articular Nodules

Under this designation several different morbid conditions have been described. The term should be reserved for the condition as originally described by Lutz and by Jeanselme (*nodosités juxta-articulaires*). So defined they consist of hard, smooth or lobulated, painless, insensible, often symmetrically placed nodes, which arise in the hypodermal connective-tissue in the neighbourhood of the larger joints and subcutaneous bony crests liable to pressure. They may be partly movable, more commonly fixed to subjacent structures, and rarely adherent to the skin. The skin covering them is normal except when changes have resulted from friction. They vary greatly in number from a single node

to a dozen or more on each side of the body; they are often grouped and may together form a mass of considerable size; individually they may be from the size of a haricot bean to that of a tangerine. They occur most commonly about the elbows, knees, ankles, the femoral trochanters, the ischial tuberosities, and the iliac spines.

Both sexes are susceptible and the nodules are most common in persons over middle age. The condition has been noted in most endemic yaws areas and may be found in as many as 2 or 3 per cent of some groups of cases, though in others the incidence is small. *Incidence*

A similar if not identical condition has been described in more recent years as occurring in syphilis, though the number of such cases in Europe is very small. The exact relation of these nodes to yaws or syphilis has not been determined. It is usually stated that treponemata are not found in the lesions, but they have recently been demonstrated in nodules due to yaws by Turner and Ferris. The contents of the node, when softening has taken place as it appears to do more commonly in the syphilitic form, are sterile.

The histological picture varies somewhat according to the stage of evolution of the node. Lying in an envelope of loose connective tissue, the nodule consists of an outer zone of dense concentrically arranged fibrous tissue, poor in fibroblasts but rich in collagen fibres with here and there collections of round cells showing in many cases a perivascular arrangement. More centrally hyaline changes and homogenization are noticeable and multinucleate swollen connective-tissue cells, like pseudo-giant-cells, may be seen. Within the outer layer an inner core is found consisting of a creamy amorphous magma devoid of cellular elements which has been likened to zinc ointment. In their earlier stages of development they respond to antiyaws or antisymphilitic treatment. *Morbid anatomy*

6.—TREATMENT

(1)—Prophylaxis

In view of the aetiology of the disease, prophylaxis must depend upon the protection of the individual from exposure to infection and protection from skin trauma and possibly insect vectors. The latter might be attained by the adoption of suitable clothing and therefore is impracticable in many native communities, the former by segregation and treatment of infective cases. In communities in which up to 100 per cent become infected, prophylaxis must largely consist of an attempt to treat all infective cases and render them non-contagious.

Since about 1925 efforts have been made in most countries where yaws is endemic to put this operation into effect. Anti-yaws campaigns have been launched on a very large scale but unfortunately, in most cases, no proper survey of the problem in hand has been made, no effective control has been established, and the results of the particular therapeutic measure have not been adequately followed, so that no very definite conclusion can be drawn as to the efficiency of these attempts at mass

treatment. To some extent these defaults are inseparable from the conditions under which these campaigns are promoted.

The stage of the disease at which treatment should be initiated, the best preparations to be used, and the most advantageous dosage and courses of treatment were questions about which little was known and concerning which knowledge lacks precision. In a single experiment it was demonstrated in a volunteer inoculated with yaws who swallowed 1 hour later 3 tablets of stovarsol and on 3 subsequent days 4 tablets per day that no infection occurred in the subsequent 8 weeks, whereas in a control monkey given the same inoculation, but no treatment, infection resulted.

In the opinion of Turner and Saunders, of the Jamaica Yaws Commission, 'the control of yaws through *curative* treatment alone is impractical if not impossible'. They suggest the only method of effecting any material reduction in the annual attack rate, and thus of lowering the incidence of the disease in any community, is by the reduction, through treatment, of the sources of infection. The methods to be adopted in making a preliminary survey of the problem and in planning the campaign against the disease have been dealt with by these authors in detail.

(2)—General Treatment

Treatment in hospital of the thousands of cases of yaws which may seek medical care is seldom possible though nursing along general lines will do much to relieve symptoms. Warm mildly antiseptic baths may be recommended. Local applications to the lesions of the secondary eruption are seldom possible or necessary as they will clear up under specific medical treatment, but for more persistent lesions gauze dressings with a mild antiseptic powder are best. Rest is advantageous and any dietetic deficiency, common enough among yaws-infected native communities, should be corrected.

(3)—Specific Treatment

All those drugs which have been used in syphilis have been tried in yaws.

Mercury

Mercurials were used, it is stated with success, in the old slave days, but fell into disuse presumably because they were found wanting. By most observers at the present time mercury is considered to have little or no action in yaws, and some hold that this difference in the effect of mercury constitutes a point of differentiation between the disease and syphilis. At all events mercury finds no place in the treatment of framboesia at the present day.

Potassium iodide

Potassium iodide may be used with advantage in the treatment of some of the late manifestations but should be so employed only after or in conjunction with arsenic or bismuth.

Arsenic

The organic arsenicals have been found to be the most potent therapeutic agents in yaws. Their action in clearing up the secondary eruption is in many cases most dramatic. This led in the earlier years of their use to the belief that yaws was a disease easy to combat. Further observations, however, showed that this was not true and that with the doses then used many cases were only rendered latent. This gave rise to the introduction of the rather unfortunate expression 'clinical cure', a phrase '*Clinical cure*' better rendered perhaps by the French word '*blanchissement*'.

Both trivalent and pentavalent compounds have been employed. Of the former *Arsphenamine* need not be discussed; the disadvantages associated with its preparation for use and the severe reactions which may follow render it inappropriate for the treatment of yaws. These disadvantages were overcome with the introduction of neoarsphenamine, *Neo-arsphenamine* or '914' also known as neoarsenobenzene, which has proved a drug of the greatest value in yaws. The best individual dose and the length of the courses of treatment necessary to effect cure still remain unsettled. The chief object of the antiyaws campaigns has admittedly been to attempt to reduce the number of infective cases in any particular area, and very few controlled results are available over any sufficient period of time.

This probably accounts for the very varied observations published. Some of them may be cited: 94.5 per cent of patients remained well one and a half months after a single injection of 0.6 gm.; 25 per cent cures (*sic*) after one and 50 per cent cures after two injections of 0.01 to 0.015 gm. per kilo body weight; 18 per cent cured (*sic*) after one and 60 per cent after two injections; two injections of 0.3 and 0.6 gm. at a week's interval were followed by no relapse during the subsequent twelve months. Other observers find that larger doses and longer courses are essential: two doses each of 0.75 gm. followed by two others of 0.9 gm. at four-day intervals; a total of 5 gm. is aimed at by others or six weekly injections of a dose of 0.05 gm. per 10 lb. body weight.

The immediate effects of treatment upon the yaw lesion and the contained treponemata have been mentioned. Two hours after a single injection of neoarsphenamine it may be impossible any longer to demonstrate the organism by dark ground illumination and none can be shown twenty hours later by staining. Within six hours the yaws granuloma often begins to clear up, in twenty-four hours the exudate has ceased, polymorphonuclear cells have disappeared, and phagocytosis may be observed; the epidermis may be almost restored and the hyperkeratosis markedly reduced.

Sulpharsphenamine (disodium - diamino - dihydroxyarsenobenzene-trimethylenedisulphite), though easy to administer by the muscular or deep subcutaneous routes, appears to have been little used in spite of the good results obtained in syphilis. *Sulpharsphenamine*

'Arsenoxide' in the form of mapharsen is of low toxicity and forms a '*Arsenoxide*'

useful remedy in syphilis in doses of 40–60–75 mgm. intravenously, but it has not yet been given a trial in yaws.

Among the pentavalent arsenicals tryparsamide finds no place in the therapy of framboesia.

Acetarsol (stovarsol) is a useful preparation in treating the disease in children. For infants and children up to 5 years the dosage is 3 tablets each of 0.25 gm. on each of two successive days; for children from 5 to 15 years, 4 tablets are given. Another method is to give 2 tablets on the first day, 3 on the second, 4 on the third, and none on the fourth; and on the fifth, sixth, and seventh 4, 3, and 2.

In adults acetarsol-sodium in 0.5, 1.0, 1.5 gm. doses intravenously at 48 hours intervals, to a total of 9.0 gm. for secondary and 15 gm. for tertiary yaws, has also been found useful.

Tablets of treparsol, 0.25 to 1 gm. daily for 4 days in succession in each of 4 weeks, may be tried.

Acetylarsan (diethylamine acetarsol), an easily eliminated compound and therefore one that can be administered in large doses of 0.02 gm. per kilo body weight subcutaneously at 48-hour intervals, is only on trial. Solganol B (an organic compound of gold), six doses of 0.1 gm. intravenously at 5-day intervals, is said to have caused the disappearance of lesions but as a treatment in yaws is of no practical importance. Tarvan (sodium vanadium tartrate) has been proposed but as yet has not been tried out in yaws.

Bismuth

Bismuth was introduced into the treatment of yaws after the demonstration of its usefulness in syphilis, and on account of its cheapness and efficacy in yaws has in many countries almost superseded arsenobenzene derivatives. It may be given as the metal or as an insoluble salt, in watery or oily suspension. The bismuth preparations which are soluble in water or in oil appear to be unsuitable for various reasons.

The oxychloride, so often used in the treatment of syphilis, in bi-weekly deep subcutaneous injections of 0.2 to 0.3 gm. does not appear to have been given the trial it deserves. In its place the salicylate, the subgallate, or double tartrate are generally preferred.

The salicylate as a 10 per cent oily suspension in doses of 0.2 c.c. per 10 lb. body weight is administered by deep subcutaneous injection at intervals of 3 to 4 days with a total of 3 to 6 injections.

The subgallate (dermatol) is given in doses of 1 c.c. of a 10 per cent oily suspension per 10 kg. body weight intramuscularly at 4-day intervals to a total of 1.5 gm. of metallic bismuth. The oxyiodo-gallate (airol) is preferred by some observers: 10 weekly injections, intramuscularly, of 1 to 4 c.c. of a preparation containing 20 gm. to 100 c.c. glycerin and water. Sodium potassium bismuthyltartrate is given as an oily suspension in doses of 0.2 gm. in 2 c.c. of diluent deep subcutaneously to a total of 3 gm. for adults; for children 0.05 gm. is given intramuscularly every 4 to 5 days to a total of 5 injections.

A suspension of precipitated metallic bismuth in a glucose or saline medium in doses of 0.15 to 0.2 gm. intramuscularly at 3 to 4 day intervals is perhaps worthy of further trial. *Bismuth metal*

Recently bisnene, a bismuth analogue of urea stibamine, has been prepared containing 50 per cent of metallic bismuth to be given at weekly intervals, 4 doses of 0.1 to 0.15 gm., but results have not yet been published. *Bisnene*

The most recently published results of controlled treatment in Jamaica are as follows. Of 1,103 cases of yaws treated with from 1 to 6 injections of neoarsphenamine (average 4) and of 858 cases treated with bismuth salicylate in the same way (average 4.5) and kept under observation for eighteen months, approximately 23 per cent showed relapse. Of the neoarsphenamine-treated patients who received only one injection 42.8 per cent relapsed; of those who received six injections 18.9 relapsed. Nearly half of the relapses occurred in the first six months after treatment. Liability to relapse tends to decrease rapidly as the number of treatments increases up to three or four and then more slowly up to six. Relapses were more frequent in areas where the rainfall was heavy and during the rainy season, a fact which should never be lost sight of when evaluating any particular treatment. *Results of neoarsphenamine treatment in Jamaica*

It has been suggested that an active immunization to yaws could be produced by the intra-mesodermal inoculation of dead treponematous material from cases of yaws, but no work along these lines has been carried out.

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YELLOW FEVER

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1.-DEFINITION AND HISTORY

1616.] Yellow fever is an acute highly dangerous febrile disease due to an ultramicroscopic virus, occurring epidemically or endemically in South America and in West and Central Africa. It is characterized by a sthenic fever followed by a quiescent period, and by bradycardia, jaundice, albuminuria, and a terminal crisis. An infection produces a lasting immunity. The disease is transmitted under natural conditions by mosquitoes, principally *Aedes aegypti*, except in certain areas in South America where *A. aegypti* is absent and other vectors take its place. It is not transmitted by contact, except under laboratory conditions; it may be contracted from infective blood or tissues.

Finlay, in Havana, from 1886 onwards constantly stated that yellow fever was conveyed by the bite of a mosquito; in 1901 Reed and Carroll

showed that the causal agent was contained in infected human serum and that it could pass through a Berkefeld filter. Some twenty-seven years elapsed before Stokes, Bauer, and Hudson proved that yellow fever is due to a virus and transmitted it to the rhesus monkey (*Macacus mulatta*). Since then other animals, such as hedgehogs and mice, have been found to be more susceptible.

*Experimental
transmission
to animals*

Infection in rhesus monkeys can readily be produced by subcutaneous or intraperitoneal injection of infected blood, or by smearing blood from a patient with yellow fever on the unbroken skin, and exactly the same disease may be produced by the bite of an infected *Aedes*. The several species of monkey which have been found to be susceptible to the viscerotropic virus are the Barbary ape (*Macacus inuus*), the rhesus monkey (*M. mulatta*), the crab-eating macaque (*M. irus*), and the brown macaques (*M. speciosus* and *M. sinicus*); in the last two the infection is not usually fatal. The new-world monkeys are not so susceptible. Marmosets usually die, but capuchin monkeys suffer from mild febrile attacks. Guinea-pigs are completely refractory to intraperitoneal or subcutaneous inoculation. The European hedgehog (*Erinaceus europaeus*) and its Sudanese congener (*Atelerix albiventris*) are extremely susceptible. It has recently been found that the sera of some cows from Europe, Africa, and India protect against yellow fever virus. It is probable that these virucidal properties are due to some physiological condition and not to a previous infection with the virus of yellow fever.

An immense amount of information has accumulated about the nature of the virus and the method of its spread, the clinical aspects and geographical distribution of the disease, and the methods of prophylactic inoculation, and many of the apparently well grounded older conceptions have necessarily been modified. The scene is changing so quickly that it is becoming increasingly difficult to present a comprehensive picture of the disease. It appears that the virus is more widely distributed than the clinically recognizable disease hitherto known as yellow fever.

2.—TYPES AND THEIR GEOGRAPHICAL DISTRIBUTION

The following terms have been sanctioned by international usage: (i) *Urban form* urban yellow fever, transmitted by *Aedes aegypti* and controllable by antimosquito measures in South America and West Africa; at present there is no evidence that any animal plays any part as a reservoir of the virus under natural conditions; (ii) *Rural form* rural yellow fever, transmitted by *A. aegypti* as above; and (iii) *Selvatic or jungle form* selvatic or jungle yellow fever, occurring independently of *Aedes* and assuming epidemic proportions in southern Brazil, Bolivia, and eastern Colombia but occurring sporadically in Magdalena (northern Brazil) and the valley of the Amazon; this form attacks only those who enter the forests. It is unknown in West Africa.

The work of the International Health Division of the Rockefeller Foundation has shown that the geographical distribution of yellow fever is more extensive than was formerly thought. In the southern portions of the United States on the Atlantic coast, especially in the city of New Orleans, and in Panama, extensive epidemics ravaged the population of the larger towns during the latter part of the nineteenth century and greatly impeded the progress of public works and general development. This was especially the case in the historic episode of the Panama Canal. In the seventeenth and eighteenth centuries yellow fever constituted the scourge of the West Indies and hampered British enterprise on the west coast of Africa. The story of these epidemics, such as those in the Spanish-American war and in the campaign in Cuba, belongs to past history.

To-day yellow fever is endemic in wide areas in Brazil as well as in Bolivia, Colombia, and Ecuador, although up to 1925 it was generally believed that yellow fever no longer persisted in South America. From 1927 to 1929 it was found to be still present in Rio de Janeiro, where formerly there had been extensive epidemics; then locally infected cases were discovered in the States of São Paulo, Minas Geraes, Rio, Bahia, Sergipe, Pernambuco, and Pará. Two unexplained outbreaks of mosquito-conveyed yellow fever were reported in Colombia and Venezuela. In 1930 the viscerotome was introduced for the purpose of obtaining liver tissue for pathological examination and animal inoculation, and the existence of jungle yellow fever was proved to exist in the Valle de Chanaan, Espirito Santo, Brazil. This jungle yellow fever, which is regarded as the more natural and permanent form, was found in an outstanding outbreak at Santa Cruz de la Serra, Bolivia (a town of 20,000 inhabitants), in the very heart of the continent, some 1,000 kilometres from any known focus of infection, and in 1933 immunity surveys showed that yellow fever, though unrecognized, had not been really absent from any part of the Amazon valley for the previous twenty years. From 1934 to 1936 it was shown that jungle yellow fever is a wide-spread, important, and fatal disease. It has recently been proved that it is conveyed by the bites of *Aedes leucocaneus*, *Haemagogus capricorni*, and certain sabethine mosquitoes. There appears to be no reason to suppose that the jungle fever and yellow fever transmitted by *A. aegypti* are not identical as the viruses have been proved to be the same, but man is an important source of infection for human beings only in the latter. A possible reservoir of the virus in jungle yellow fever exists in monkeys and opossums. A certain proportion of South American and West African monkeys (about 20 per cent) show a natural immunity to the virus of yellow fever, and do not appear to play any part in its dissemination.

In Africa, Sawyer, Bauer, and Whitman have shown, as the result of immunity surveys, that yellow fever is very widely, but irregularly, distributed in a region extending from the coast of Senegal eastward for approximately 3,300 miles to the upper reaches of the White

Nile in the Anglo-Egyptian Sudan. The northern boundary is the Sahara; on the west and south the boundary follows the Atlantic from Senegal to the extreme north of Angola; the eastern boundary is formed by the western half of Uganda and the White Nile and extends across Angola to the southern part of the Belgian Congo. The area has a maximal width of about 1,400 miles and lies between the latitudes of 16° N. and 6° S. Why the disease has not spread to Kenya and Uganda is unknown.

Sporadic outbreaks of urban yellow fever continue to give grave concern in West Africa. In 1935 there was an epidemic in Bathurst on the Gambia, which was investigated by Findlay. During 1937 it was rather more common than before. Small epidemics occurred at Accra and Mepom in the Gold Coast and in Nigeria, and isolated cases have been notified at Brazzaville and Bangui in French Equatorial Africa. In the Anglo-Egyptian Sudan it has been found that 70 to 80 per cent of sera give a positive mouse-protection test in some villages in the region of the Nuba mountains. In South America it has been reported from Colombia and Peru as well as from Brazil.

*Urban form
in Africa*

*In South
America*

A number of isolated cases of laboratory infections among workers engaged in investigating the virus have been recorded. Berry and Kitchen collected thirty-five cases, but since the introduction of an efficient prophylactic method of immunization, these laboratory accidents have ceased.

*Laboratory
infection*

In the past it is recorded that yellow fever has been imported by ships into Portugal, Spain, and Italy, and even to the seaport towns of France and Great Britain, but the disease has never spread inland. Concern is now felt that, with the advent of the aeroplane and motor car and the opening up of roads in the Dark Continent and in South America, yellow fever may be introduced into India or China, where immunity tests have shown that the disease has never existed, at least in historic times.

*Spread by
transport*

3.—EPIDEMIOLOGY AND IMMUNITY

It has been stated in the older works dealing with the epidemiology of yellow fever that it is especially liable to break out and spread in the squalid and insanitary surroundings of the wharves and quays of the larger seaport towns, and until recently it appeared to be true that yellow fever was indeed a disease of the seaboard and seldom spread inland and that when it did so it tended to follow lines of communication. In former times it often occurred epidemically in sailing ships on the high seas and spread from one ship to another while they were lying in port off the coast of Portugal and southern France. Now it is understood that it may break out in a dry climate, such as that of northern Nigeria, or in the humid steaming atmosphere of the forests of the Amazon. Yellow fever requires for its dissemination a mean

atmospheric temperature of 75° F., and it does not extend its range beyond 40° north and 35° south. That urban yellow fever cannot continue to exist or spread in a locality where the mosquito is not present in sufficient numbers appears to explain many historic instances in which no special antimosquito measures have been employed and yet the disease has disappeared.

The virus can enter the body through unbroken skin and so yellow fever may follow handling infective material. Two hospital infections have been recorded in laboratory technicians making blood-slides and performing biochemical examinations on blood withdrawn from the veins in the initial stages of the fever (Low and Fairley). Severe and fatal infections have also resulted from performing necropsies on infected monkeys.

Prolonged residence in an endemic area of yellow fever does not lead to immunity, and the indigenous natives who pass unscathed through an epidemic do so not because of any inherent protective attributes but because of a previously acquired and, it may be, a mild or aborted attack. After the subsidence of an epidemic it can, in fact, be shown that the number of persons who give a positive reaction to mouse-protection tests (see p. 669) is very much greater than the number of those who presented the clinical manifestations of yellow fever.

When the virus of yellow fever is inoculated into rhesus monkeys they die before they have had time to elaborate immune bodies and therefore in a highly infective state. In human beings antibodies develop much more quickly so that at the time of death, at the fifth or sixth day of fever, sufficient immune bodies have formed to make their tissues no longer infective. The serum of patients who have recovered from yellow fever contains antibodies which protect them for the rest of their lives as has been abundantly proved by the Rockefeller Commission's researches in Nigeria.

The immunity produced by one attack of yellow fever is permanent for the rest of the patient's life. The virus has been shown to exist in the human body for about 107 hours from the onset of the fever, and antibody appears about 80 hours from the onset; thus virus and antibody can co-exist for 20 hours or more.

4.—VIRUS AND VECTORS

The yellow fever virus exists in the circulating blood in an ultramicroscopic and filterable form and passes through Berkefeld filters V and W. Findlay and Broom (1933) showed, by filtration through collodion membranes, that the size of the virus particles is approximately between 18 and 27 m μ . As shown by Sellards and Hindle, it can retain its vitality when suitably preserved in a proper state and even, when dried, can survive for many months.

The virus of yellow fever is pantropic in the sense that it can produce

lesions in all three embryonic layers. All strains, however, show two major tissue-affinities—viscerotropic and neurotropic. The viscerotropism or neurotropism can be increased under certain conditions. Thus, as shown by Theiler, the virus, when injected intracerebrally into mice, produces encephalitis and, after repeated passage in mouse brains, becomes highly neurotropic; on subsequent subcutaneous injection into susceptible rhesus monkeys it does not give rise to viscerotropic lesions but the animals remain protected. If injected into monkeys intracerebrally it produces encephalitis. At the same time, the mortality rate in mice injected intracerebrally is not diminished, though the incubation period is markedly prolonged. Findlay and Clarke (1935) showed that under certain laboratory conditions it is possible to reconvert a neurotropic strain into the ordinary viscerotropic type.

Viscerotropic and neurotropic affinities

Production of neurotropic strain

Reconversion to viscerotropic strain

Elmendorf and Smith showed that the virus can be successfully grown on the chorio-allantoic membrane of the chick embryo. When the virus is grown in serum Tyrode medium containing either minced chick or mouse embryo, the pathogenicity to monkeys of the pantropic strains on subcutaneous or intraperitoneal inoculation is greatly reduced, and neurotropism is not increased on intracerebral injection.

Cultivation on egg membranes and in tissue culture media

For the purposes of study and also for the preparation of protective vaccines, the virus can be concentrated by an ultra-centrifuge which is run regularly at 60,000 revolutions per minute and in which the rotor is placed in a high vacuum. Complete sedimentation of the virus is not obtained and a small proportion remains in the supernatant fluid even when the haemoglobin has been separated out. The virus so obtained is inactivated in distilled water and in physiological saline solution. Hence all suspensions should be made in monkey serum or in ascitic fluid. Both the viscerotropic and neurotropic strains are inactivated by a temperature of 60° to 65° C. and by photodynamic action and dyes, such as methylene blue or proflavine, or exposure to a pointolyte light. On the other hand they can withstand strong disinfectants, such as mercuric chloride (1 in 7,500) and phenol (1 in 150).

Concentration by ultra-centrifugation

Inactivation of virus

Resistance to disinfectants

The incubation period of yellow fever rarely exceeds four or five days; the limit appears to be about thirteen or fourteen. A period of twelve days must elapse, after the mosquito has had a meal of infected blood, before the virus can be effectively transplanted to another human being. This, the extrinsic incubation-period, appears to be the exact time which the virus takes to develop in the body-cavity of the mosquito; but this period has been found to vary with the temperature and the strain of the virus, being slightly longer with those obtained from the South American jungle. Therefore a period of at least a fortnight elapses between the recognition of yellow fever in a patient in a district (hitherto considered immune) and the occurrence of the first case which presages an epidemic. Therefore, in order that yellow fever can continue to exist and spread in a population, the following conditions are necessary: (i) the specific virus; (ii) a suitable vector; and (iii) susceptible human beings living under conditions in which virus and

Conditions necessary for spread of disease

man are accessible to the *Aedes* mosquito. This is generally recognized as occurring in the urban form of the disease.

Vector

The optimal temperature for the development of the virus within the body-cavity of the mosquito is 26° C., the extremes being 18° to 37° C., which correspond with the mean temperature of those regions in which yellow fever is endemic. Under natural conditions it appears that the percentage of mosquitoes which become infective is extremely small.

Mosquitoes acting as vectors

The principal vector is *Aedes aegypti*. The female insect does not lay eggs until she has had a complete blood-meal, and then deposits them within a period of three days from the date of feeding. It has recently been thought that other species of mosquito, under laboratory conditions at any rate, can transmit the virus. In northern Nigeria

Species which have acted as vectors under experimental conditions

Mansonia africana may possibly act as a vector. The following mosquitoes have been found able to transmit yellow fever by biting, under laboratory conditions. (i) Mosquitoes with universal distribution: *Aedes aegypti* and *Culex fatigans*. (ii) European mosquitoes: *Aedes geniculatus*. (iii) African mosquitoes: *Aedes vittatus*, *A. luteocephalus*, *A. africanus*, *A. simpsoni*, *A. stokesi*, *Mansonia africana*, *Culex thalassius*, and *Eretmopodites chrysogaster*. (iv) Asiatic mosquitoes: *Aedes albopictus*. (v) South American mosquitoes: *Aedes fluviatilis*, *A. scapularis*, *A. leucocaneus*, *Haemagogus capricorni*, and, very feebly, *H. janthinomys*. In general aëdines are crepuscular and non-aëdines nocturnal in their habits.

Incubation period in mosquito

The incubation period, the period before a mosquito becomes infective, depends mainly upon the temperature. At 37° C. four days suffice; at 21° C. eighteen days; but at lower temperatures, 10° to 15° C., the virus persists in the body-cavity of the mosquitoes without their bite being infective. The development of the virus appears to be simple,

Development of virus in mosquito

the body-cavity of the mosquito acting as a sort of culture medium for, if infective mosquitoes are ground up and fed in a syrup to normal mosquitoes, they too become infective after the usual incubation period. Aragão has shown that the virus is present in the alimentary canal of the insect for ten days after an infective meal of blood but that subsequently it becomes centred in the salivary glands.

5.—PATHOLOGY AND MORBID ANATOMY

Biochemical changes

The biochemical changes in yellow fever can be interpreted as interference with the liver function by the action of the virus. There is a loss of glycogen from the liver and a reduction in the blood sugar. In infected rhesus monkeys there is an increase in the blood of guanidine-like substances. The morbid changes in the liver are held to be so characteristic that it is possible to arrive at a diagnosis by microscopical section alone. The organ is friable and of a yellowish colour which has been compared to that of boxwood. The cytoplasm undergoes, in whole or in part, hyaline degeneration in which the tissue stains

Morbid changes in liver

intensely with eosin. In a small number of cells the nucleoplasm is occupied by acidophilic intranuclear masses of inclusions, Councilman bodies, which are similar to those in other virus diseases. The liver cells are often separated from one another and tend to assume a rounded shape. The necrotic changes in the liver cells have been known as hyaline necrosis and produce an appearance of intense fatty degeneration. The most marked changes were found in the mid-zonal region of the liver lobules. The kidneys show haemorrhagic foci under the capsule and the renal epithelium undergoes cloudy swelling which passes on to fatty degeneration. The tubules here and there are filled with lime casts. There is a slight leucocytosis early in the disease, followed by a leucopenia. At first the polymorphonuclear cells predominate but there is a rise in the mononuclears during convalescence.

*Councilman
bodies*

In kidneys

*White blood
count*

6.—CLINICAL PICTURE

Recent experience has shown that yellow fever presents a wide variation of symptoms and that the external signs have little relation to the virulence of the infecting agent. The illness may begin insidiously with a slight chill. Beeuwkes, in an analysis of mild cases, reported that the most constant symptoms were headache, pain in the back and extremities, photophobia, anorexia, prostration, congestion of the eyes, and a tongue coated in the centre with red edges and tip. In these mild cases the illness passes off within five to six days without vomiting, icterus, albuminuria, or any resemblance to the very terrible disease true yellow fever.

Mild cases

In acute yellow fever the initial fever is sudden and lasts three to four days. The temperature reaches its maximum in the first twenty-four hours and may rise to 103° or even 104° F., but during the subsequent three or four days it falls and becomes normal or even sub-normal. From the onset headache is the chief feature; for the most part the pain is concentrated on the forehead and referred to the eye-balls and in most cases there is photophobia. Pain in the loins is prominent and may be as severe as that of smallpox. There are also intense pains in the bones, especially in the ankles. Epigastric pain is also noticeable. The eyes are pink and bloodshot and have a 'ferret' look. The face is flushed and swollen. The skin throughout the fever remains hot and dry. In the early stages the pulse-rate varies from 100 to 120 and is of the typical febrile type, full and strong; but during the 'period of calm' it becomes remarkably slow and easily compressible—a typical bradycardia of 30 to 40 beats a minute. This falling or constant pulse-rate with a rising temperature constitutes 'Faget's sign'. The tongue soon becomes coated on the dorsum but the edges remain clean, and it remains small and pointed throughout the disease. In serious or fatal cases the tongue becomes dry, and thirst is intolerable, at the same time there may be bleeding from the gums.

Acute cases

Temperature

*Headache
and pain*

Facies

Pulse

*'Period of
calm'*

'Faget's sign'

Tongue

By the third day the sclerotics show an icteric tinge and usually the

Jaundice

- skin assumes the bright yellow tint from which the disease derives its name; but this is not seen in every case. In fatal cases the discoloration becomes intensified and may become a deep mahogany brown, when it emits a peculiar odour which has been compared to that of a fish-market. Petechial subcuticular haemorrhages may also occur and give a blotchy blue or violet appearance. An erythematous condition of the vulva or scrotum is often noted.
- Petechial haemorrhages*
- Nausea and vomiting are almost invariable. In the earlier stages bilious vomiting is common; later there occurs the 'black vomit' which is regarded as a fatal sign. This vomit, which is intensely acid, consists of broken-down blood-corpuscles suspended in a yellowish mucoid fluid. Sometimes there is a frank haematemesis but similar haemorrhages may occur from almost any orifice.
- Black vomiting*
- Haematemesis*
- Albuminuria is present from the outset and is an important feature from the point of view of both diagnosis and prognosis. Should the exudation of albumin become excessive, suppression of urine may occur. In severe cases the amount of urine passed may fall to a few ounces; it is very acid and may contain bile pigments and bile-stained tubular casts from the fifth day onwards.
- Albuminuria*
- Insomnia is usually present from the start but delirium is uncommon.
- Insomnia*
- Restlessness marks the initial period, torpor or coma the end. A well marked tache can be demonstrated on the forehead and sometimes also on other portions of the body.
- Coma*
- Death may occur in the early acute stage, being usually presaged by hyperpyrexia, but most deaths occur on the fifth or sixth day. It has often been remarked that death seldom occurs before the third and rarely after the eleventh day.
- Death*
- In mild cases the 'period of calm' which sets in after the subsidence of the initial fever may usher in convalescence. In severe cases the phase is followed by a third stage which is known as the 'stage of reaction'—a remitting fever of an adynamic type, which persists for several days or weeks. Should there be any complications, such as boils, parotitis, or buboes, this may be of long duration. In the period of reaction the icterus becomes more pronounced and black vomit recurs.
- 'Period of calm'*
- 'Stage of reaction'*
- Relapses are very rare but when they occur are extremely severe.
- Relapses*

7.—PROGNOSIS

Initial rigors, convulsions, diminution in excretion of urine, coma, and haemorrhages are all regarded as unfavourable. On the other hand, prognosis is good if the temperature in the initial fever does not exceed 103° to 105° F. According to Sternberg, in cases in which the temperature rises to over 106° F., there are no recoveries. The mortality among newcomers, or the unacclimatized, ranges between 25 and 30 per cent, but among the permanent indigenous inhabitants it is much lower, 7 to 10 per cent.

8.—DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Within the first three days of the fever the virus is readily transmitted by inoculation of blood into rhesus monkeys, but it is much cheaper and more convenient to inoculate infective blood intracerebrally into white mice, in which the characteristic encephalitis is produced within seven to fifteen days. In fatal cases yellow fever is diagnosed histologically by detection of the characteristic changes of the liver. In recovered cases the mouse-protection test may be employed.

'Protection tests', which can be used for the diagnosis of yellow fever in patients who have recovered from the disease, are based on the fact that after an attack of yellow fever immune bodies are abundant in the serum during life, and that when admixtures of immune serum and virus are injected into susceptible animals infection does not occur. A positive 'monkey-protection test' denotes that the animal survives after the injection of a mixture of the viscerotropic virus and the serum. When the neurotropic virus is employed, a mixture of the serum and infected mouse brain is injected into mice subcutaneously and at the same time the animal is inoculated intracerebrally with starch. If the serum fails to protect, the mice develop encephalitis; this is known as the 'mouse-protection test'. Both these tests have been proved to possess a high degree of specificity and the results obtained with them in the same areas of Africa and South America have been shown to be in close agreement.

Severe yellow fever must be distinguished from the pernicious forms of subtertian malaria (the bilious remittent forms), blackwater fever, and infective jaundice (spirochaetosis icterohaemorrhagica) and other forms of jaundice, especially infective hepatitis (catarrhal jaundice). The usual methods of blood examination serve to exclude subtertian malaria unless there is, as sometimes happens, a concomitant malarial infection. Dengue, influenza, and, in Kenya, Rift Valley fever closely resemble the mild or abortive forms of yellow fever, and relapsing fever is not uncommonly diagnosed as yellow fever. When several deaths have occurred in a district within a few days of each other, and especially when they have been preceded by fever and black vomit, the suspicion of yellow fever becomes a certainty.

9.—TREATMENT

In the urban type of yellow fever prophylaxis is directed towards the extermination of mosquitoes, especially the domestic-breeding *Aedes aegypti*. This entails a knowledge of the habits of this insect. All empty tins and vessels in the neighbourhood of dwellings must be destroyed and the harbouring of pails of rubbish strictly forbidden. All water tanks, gutters, and cisterns must be effectually screened and all puddles

and stagnant pools filled in. The use of mosquito-nets should be made compulsory.

*Precautions
against aerial
transport of
disease*

*Prophylactic
inoculation*

*Dangers in
use of
neurotropic
virus alone*

*Use of
cultured
pantropic
virus*

*Jaundice
following
inoculation
after interval*

*General
treatment*

*Immune
serum*

Purging

*Calcium
lactate*

*Glucose and
insulin*

Special measures have become necessary in recent years on account of the increase of aviation and have been sanctioned by an International Sanitary Commission for Aerial Navigation. Prophylactic inoculation as a practical measure of immunizing visitors and residents in an endemic area of yellow fever is now being widely undertaken. The original method was based on the fact that the yellow fever virus, when it has become fixed for mouse brain by repeated intracerebral inoculations, fails to produce viscerotropic lesions. American and English workers added sufficient immune human serum to counteract the possible circulation of the virus in the blood-stream. In France, however, Laigret has used the neurotropic yellow fever virus obtained from mouse brain either alone or mixed with egg-yolk or bile. Some thousands of persons have been immunized by this method; not only may the immediate reaction be extremely severe, but a very considerable number of cases of involvement of the central nervous system have been reported. The use of the neurotropic virus alone is therefore too dangerous to be recommended. At present both in England (Findlay and MacCallum, 1937) and in America the attenuated pantropic virus, cultivated in serum Tyrode medium containing minced chick embryo, is now solely employed. At first the virus inoculum was combined with human immune yellow-fever serum, but since 1936 the virus alone has been injected and some thousands of persons have now been immunized without any serious reaction.

Findlay and MacCallum also drew attention to a peculiar form of jaundice, resembling epidemic hepatitis, with an enlarged and tender liver, which may develop two to seven months after yellow-fever inoculation and which takes usually five to six weeks to clear up. About ninety cases have been noted in a series of 3,100 inoculations. With a change of the strain of the virus no further cases of jaundice have occurred among more than 2,000 persons immunized. The explanation of this curious complication is almost certainly that some extraneous hepatotoxic agent of a virus-nature was injected with the yellow-fever virus.

It is now generally recognized that in the treatment of yellow fever general measures and nursing are more important than drugs. The patient must be nursed in bed throughout. The injection of immune serum is the one potent measure available, and this is only of value during the incubation period when it may decrease the severity of the disease. A purgative from the onset, such as castor oil, is beneficial. Hot mustard pediluvia have acquired a reputation for relieving the intense headaches. During the high fever frequent tepid spongings, or even cold baths, may be employed carefully. Calcium lactate in large doses by mouth is probably of value in counteracting the excess of guanidine in the blood. Glucose is indicated, as in other hepatic conditions, and injection of 5 units of insulin improves its assimilation.

Glucose should be given in 1 drachm doses by the mouth, but when nausea and vomiting are present amounts of 10 fluid ounces or more of 5 per cent solution of glucose should be injected intravenously. Water, lemonade, or barley water should be freely given to counteract the failure of renal function. For the first three days all food by mouth should be withheld. When the appetite returns small quantities of bland food, such as teaspoonfuls of albumen water, iced milk, or chicken broth, should be permitted and gradually increased. Nutrition may be aided by nutrient enemas. As regards specific treatment the method of Sternberg has gained a high reputation. This is directed to counteract the acidity of the gastric and intestinal contents by a mixture of 150 grains of sodium bicarbonate and $\frac{1}{3}$ grain of mercuric chloride in a quart of water; $1\frac{1}{2}$ fluid ounces of this are given every hour.

Fluids
Diet

Sternberg's treatment

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ZONDEK-ASCHHEIM REACTION

See PREGNANCY, Vol. X, p. 62

ZOSTER

See HERPES, Vol. VI, p. 513

NOTE

An exhaustive analytical index to the *British Encyclopaedia of Medical Practice* follows the completion of this work. In the volume index below, each individual title is separately indexed in the volume to which it belongs, and there are additional references and cross-references to assist the reader in finding whatever information he may require as easily and quickly as possible.

The entries in heavy type (e.g. **Tetanus**) indicate the individual titles; those in large capitals (e.g. **ABDERHALDEN'S TEST**) indicate the additional references and cross-references.

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